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# URTICARIAL REACTION INDUCED IN THE DOG BY INTRAVENOUS INJECTION OF SORBITOL MONOLAURATE

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DURING the course of experiments on parenteral nutrition in the dog, H. C. Meng and Smith Freeman [1] observed that the slow intravenous injection of a fat emulsion, stabilized with sorbitol monolaurate (tween 20®), was associated with the development of urticaria. This observation prompted us to undertake a study of the changes which might be related to the development of urticaria, since no other pure substance is known to us which on intravenous injection will consistently cause urticaria. The chemical does not cause urticaria when given orally but does so when introduced intradermally, without previous sensitization of the animal.

In order for one to determine the relation of this experimental urticaria in the dog to that which is produced in man, it will be necessary to review briefly what is known regarding the nature of urticaria in man.

## SUMMARY OF KNOWLEDGE OF THE URTICARIAL REACTION

The urticarial reaction consists essentially of three local changes in the skin, which Lewis [1a] has referred to as "the triple response." The triple response consists (1) of a red area, which within a few seconds becomes surrounded (2) by a flare or flush, after which (3) a wheal begins to appear. The wheal soon becomes pale and usually disappears within an hour.

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1. Meng, H. C., and Freeman, S.: Experimental Studies on the Intravenous Injection of Fat Emulsion into Dogs, J. Lab. & Clin. Med. **33**:689-707, 1948.

1a. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1926.

This triple response may be produced experimentally in human skin, and in the skin of some animals, in response to mechanical injury, heat and cold and the intracutaneous introduction of many substances, such as histamine, allergens, morphine, codeine, physostigmine, pilocarpine and atropine. It is generally agreed, however, that whealing is a specific response to certain substances, because all substances do not give the response.

*Histologic Characteristics.*—Histopathologically, the urticarial reaction is a mild inflammation [2] which is remarkably reversible, since the production of a morphine wheal thirty-five times at the same site over the period of several days did not produce any evidence of chronic histologic change.[2d] When the reaction is produced by the intradermal introduction of ragweed pollen into a person sensitive to this pollen, the changes which occur are as follows: After five minutes the blood vessels are engorged, slight edema is evident, and a few leukocytes have collected in the engorged minute vessels. After ten minutes the edema has increased to a maximum and there is pronounced intravascular collection of polymorphonuclear leukocytes. After fifteen minutes there is moderate engorgement except in pale areas; edema is appreciable, and wandering cells and leukocytes are in the surrounding tissues; 25 per cent of the leukocytes are eosinophils. After twenty minutes the principal addition to the prior changes is an increase in eosinophils to 50 per cent. At a variable time, after four hours according to Kline and associates [2b] and after twenty-four to forty-eight hours according to Berger and Lang,[2c] the eosinophils have appreciably decreased in number.

Histamine introduced intradermally into allergic persons tends to produce histopathologic changes like a specific allergen,[2b] whereas in the nonallergic person it causes vascular changes and edema, and very little leukocytosis.

The intravascular behavior of leukocytes in an antigen-antibody reaction in the rabbit, as demonstrated by Abell and Schenck,[1e] is of much interest. When horse serum is applied to the minute vessels of the ear of a sensitized rabbit, the vessels being visualized by a special technic, the vascular endothelium develops stickiness for leukocytes, which collect in clumps and pass through the wall of the vessel. This behavior is significant because leukocytes contain histamine and thromboplastin.

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2. (*a*) Numa, P. G.: The Histopathology of Diseases of the Skin, New York, Macmillan and Company, 1896. (*b*) Kline, B. S.; Cohen, M. B., and Rudolph, J. A.: J. Allergy **3**:531, 1932. (*c*) Berger, W., and Lang, T. J.: Ztschr. f. Hyg. u. Infektionskr. **113**:206, 1936. (*d*) Török, L., and Hare, P.: Arch. f. Dermat. u. Syph. **65**:2, 1903. (*e*) Abell, P. G., and Schenck, H. P.: J. Immunol. **34**:195, 1938.

*Physiologic Aspects.*—Physiologically, the mechanism of the formation of the red spot, the surrounding flare and the wheal has been studied extensively, particularly by Lewis and his colleagues.[1]

The red spot surrounding the site of introduction of the urticariogenic agent is due to the direct dilating action of the agent, or something produced by the agent, on the blood vessels. It occurs in the denervated skin after time has elapsed to permit degeneration of nerve fibers.[1]

The diffuse flare surounding the red spot and, later, the wheal, is due predominantly[3] to an axon reflex, since it occurs in an area of skin during the first five or six days after section of its nerve supply, but not afterward, the wheal but not the flare occurring then.[1]

The wheal, which begins soon after the appearance of the flare, is usually confined to the area of the red spot or to those vessels most directly influenced by the injected agent or something produced by it. The wheal is due to an increase in capillary permeability. This fact is shown by the coloring of the wheal after the intravenous injection of dyes (trypan blue or trypan red, congo red, Evans blue and rose bengal), which ordinarily do not stain the skin.[4] This coloring occurs only if the dyes are injected intravenously soon before or at the time the wheal forms. It fails to occur if the dye is injected after the wheal has turned pale because of vascular occlusion secondary to the presence of the edema. The increased permeability is also demonstrated by the presence of protein in the wheal fluid in a concentration which approximates that of plasma.[5] Formation of a wheal is not due to local vasodilatation, per se, because intense local dilatation may be caused by the introduction of methacholine chloride (mecholyl chloride®) or acetylcholine by needle or electrophoresis without the formation of a wheal or a change in permeability.[6] The formation of the wheal is not due to increased pressure in or distension of the capillaries. One can demonstrate the validity of this statement easily by placing a sphygmomanometer cuff on the arm, raising the pressure in the cuff up to 30 or 50 mm. of mercury and then introducing histamine into the skin.[1] This procedure, of course, increases the venous and capillary pressure, yet

3. Goldschmidt, S., and M'Glone, B.: Proc. Soc. Exper. Biol. & Med. **29**:827, 1932.

4. Ebbecke, U.: Klin. Wchnschr. **2**:1725, 1923. Hoff, F.: Ztschr. f. d. ges. exper. Med. **57**:253, 1927. Ferrebee, J. W., and Berliner, P. W.: Proc. Soc. Exper. Biol. & Med. **46**:549, 1941.

5. Lewis.[1] Török, L.: Arch. f. Dermat. u. Syph. **53**:243, 1900. Stead, E. A., and Warren, J. W.: J. Clin. Investigation **23**:279, 1944.

6. (*a*) Rocha E. Silva, M., and Dragstedt, C. A.: J. Pharmacol. & Exper. Therap. **73**:405, 1941. (*b*) Last, M. R., and Loew, E. R.: ibid. **89**:81, 1947. (*c*) Alexander, H. L.; Elliott, R., and Kirchner, E.: J. Invest. Dermat. **3**:207, 1940.

the wheal is the same or smaller in size than usual, and it becomes progressively smaller until the systolic pressure is reached. On complete occlusion of the blood supply the wheal does not occur, but if the occlusion is released within five minutes after the introduction of histamine the wheal occurs. The results of such experiments as those just described unequivocally prove (*a*) that the wheal is associated with the local increase in permeability of the capillaries, (*b*) that its formation is dependent on an adequate flow of blood and (*c*) that its formation is not dependent solely on a high venous pressure.

In whealing, the lymphatics also become more permeable, and their efficiency of drainage is decreased by the pressure block caused by the edema fluid.[7]

Some animals do not manifest whealing. Wheals do not develop in rabbits, cats and guinea pigs when histamine or other wheal-producing substances are introduced intradermally.[8] In the dog, goat, horse and man, they do. However, histamine increases the permeability to dyes of the capillaries in rabbits, cats and guinea pigs. Whether this failure of certain animals to manifest whealing is due to structural or to physiologic differences in the skin is uncertain.

Some substances cause local vasodilatation without flare and whealing, regardless of concentration. Other substances and procedures cause vasodilatation without whealing when the concentration or intensity is relatively high. This difference could be explained as due to the possibility that some substances or procedures are more injurious to the capillary wall than are others.

The concept that the wheal and flare are due to the release of a substance by the cells of the skin when they are injured was derived from many experiments performed by Lewis.[1a] We shall cite a few of his experiments. The circulation to the arm is impaired first with a pressure of 30 mm. of mercury to cause congestion and then to 200 mm. mercury for occlusion; histamine is introduced intradermally; the skin is covered with petrolatum U. S. P. and warmed to 20 C. with water and the histamine theoretically is permitted to diffuse for five minutes. During the occlusion a small area of local vasodilatation occurs at about the point of injection, and on release of the occlusion the area doubles in size, this development obviously indicating that diffusion has occurred. Now, if the experiment is repeated, the skin of an urticarial subject having dermographism being stroked, the purple line formed by the stroke, as well as the wheal which occurs after release of the occlusion, can be seen to spread. Also, if two wheals and

7. (*a*) Hudack, S., and McMaster, P. D.: J. Exper. Med. **56**:223, 1932; **57**:751, 1933. (*b*) Abramson, H. A., and Engle, M.: J. Invest. Dermat. **1**:65, 1938.

8. Darsie, M. L.; Perry, S. M.; Rosenfeld, D., and Zaro, J. D.: Proc. Soc. Exper. Biol. & Med. **59**:278, 1945.

flares are produced on an arm, one above the other, and the circulation to the lower one is occluded, the flare of the one without occlusion will fade, while the other flare will persist until the occlusion is released. This experiment shows that the cause of the flare is either washed away or destroyed by the blood. To show that a vasodilator substance may enter the blood in urticaria, in a patient with urticaria factitia the smallest dose of histamine given subcutaneously which would cause flushing of the skin was determined. The skin of the patient was then stroked to produce whealing in several areas, and flushing occurred. There are also a number of articles in the literature which show that whealing of the skin produced by various means, mechanical and caloric,[9] stimulates gastric secretion. The foregoing experiments indicate the formation of a substance that diffuses rather rapidly. Lewis and his colleagues performed another experiment in which it was found that a more slowly diffusing substance was produced. When a restricted area of the skin is exposed to an erythema dose of ultraviolet light, the red area is much larger at twenty-four than at six hours.

Thus there is evidence which indicates that on injury of the cells of the skin (*a*) a rapidly diffusing substance analogous to histamine, which dilates and increases the permeability of minute blood vessels, is formed, and (*b*) a slowly diffusing substance (H colloid) may be formed. It need not be assumed on the basis of the evidence that only histamine or only one H substance is produced.[10] The nature of the vasodilator may vary with the agent involved in its production. That this statement is true is indicated by the results of experiments performed on refractoriness and antihistaminic drugs, to be mentioned later.

Is histamine directly involved in causing the flare and wheal? Histamine is present in the skin.[11] Lewis and his colleague [1a] were able to obtain enough wheal fluid to demonstrate on its injection into the skin the occurrence of a flare and wheal like those caused by histamine. But Abramson and Engle [7b] were unable to isolate histamine from

9. Baker, T. W.: Histaminase in Treatment of Cold Allergy, J. A. M. A. **114**:1059 (March 23) 1940. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold, with Local and Systemic Manifestations of Histamine-Like Character: Its Amenability to Treatment, ibid. **107**:1263 (Oct. 17) 1936.

10. Krogh, A.: The Anatomy and Physiology of the Capillaries, New Haven, Conn., Yale University Press, 1929. Rous, P., and Gilding, B. M.: J. Exper. Med. **51**:27, 1930.

11. Best, C. H., and McHenry, E. W.: Physiol. Rev. **11**:379, 1931. Rose, B., and Brown, J. S. L.: Am. J. Physiol. **124**:412, 1938. Rosenthal, S. P., and Minard, D.: J. Exper. Med. **70**:415, 1939. Marshall, P. B.: J. Physiol. **102**:180, 1943. Alexander, F.: Quart. J. Exper.-Physiol. **33**:71, 1944.

wheals caused by ragweed pollen. They do not interpret this finding as proving that histamine is absent from the fluid or the process which caused the whealing. Nevertheless, there is no direct evidence that histamine is released in the urticarial reaction.

Is acetylcholine directly involved in causing the flare and wheal? Grant, Pearson and Comeau [12] suggested that cholinergic nerves were involved in the urticaria which occurs in association with emotion, exercise and warmth. They made this suggestion because in such conditions urticaria could be induced by pilocarpine and choline derivatives and improved by atropine. However, considerable evidence has been presented against the view that acetylcholine is concerned in the mechanism of the production of urticaria. Acetylcholine introduced into the skin by electrophoresis causes only local vasodilatation.[6c] It has not been demonstrated that acetylcholine is produced by antidromic (posterior root nerves) or axon reflex impulses.[13] Atropine has no effect on the wheal and flare induced in man by allergens. [14] On the contrary, Lewis [15] more recently reported that wheals develop in many women on the electrophoretic introduction of acetylcholine. It is possible that in a susceptible person the vasodilatation induced locally by acetylcholine predisposes to the development of a wheal in the same way that vasoconstriction tends to reduce whealing.[16] On the basis of the evidence, it is a likely hypothesis that the release of acetylcholine is a part of the causative mechanism of urticaria associated with exposure to emotion, exercise and warmth.

*Refractoriness to Triple Response.*—Due to Histamine: Lewis [1a] showed quite clearly that for a period from fifteen up to thirty or sixty minutes after blood vessels have been exposed locally to the action of histamine the vessels are refractory to a second exposure to histamine as regards formation of the wheal but not of the flare. For example, if the blood supply of an arm is occluded, and histamine is introduced intradermally at site A and site B, and the arm kept warm at 33 C. for fifteen or twenty minutes, and then, before the occlusion is released, histamine is introduced again into site B but not into site A, on release of the occlusion, a wheal does not occur at site A, and no wheal, or only a slight one, occurs at site B, though a flare occurs. This experiment shows that the vessels at site B have become refractory to whealing but not to flare.

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12. Grant, R. T.; Pearson, R. S. B., and Comeau, W. J.: Clin. Sc. **2**:253, 1936.

13. Doupe, J.; Cullen, C. H.; Macaulay, L. J.; Sharp, M. E.; Barnes, R., and Kerr, A. S.: J. Neurol. & Psychiat. **6**:94, 1943.

14. Tuft, L., and Brodsky, M. L.: J. Allergy **7**:238, 1936.

15. Lewis, T.: Clin. Sc. **5**:5, 1944.

16. Loew, C. R.: Physiol. Rev. **27**:542, 1947.

If a histamine wheal and flare are induced in the same site every thirty minutes, the site becomes refractory to whealing.[1a] If an hour elapses between the induction of the wheal and that of the flare, the site does not become refractory to whealing after 10 or 12 trials, whether the histamine is introduced by needle or by electrophoresis.[17]

Thus, refractoriness to the effect of histamine in increasing the permeability of capillaries lasts only ten to thirty minutes.

Due to a Mechanical Stimulus: If a stroke stimulus is applied to the skin of a patient with urticaria factitia and then, fifteen or thirty minutes later, when the wheal has started to subside, a second stroke is applied so as to intersect the wheal of the first, a wheal does not develop at the intersection. The time element in this experiment is analogous to the refractory period of whealing induced by histamine.

Due to Physical Agents: When the skin is injured by heat, freezing, ultraviolet light or roentgen rays to the point that some erythema and edema result, flare, but not whealing, occurs in response to histamine.[18] Shaffer[19] has found that doses of roentgen radiation (125 r) which do not cause visible injury induce a refractoriness to histamine whealing forty-eight hours after exposure and continues for four days.

Due to Allergens.—In patients with chronic urticaria wheals do not ordinarily occur in the same site until thirty hours or more have elapsed. Nevertheless, the introduction of histamine into such a refractory site produces a wheal. This reaction shows that in this case the blood vessels are not refractory to whealing.

However, during the subsidence of a wheal caused by an allergen (fish), the site is refractory to histamine for ten or twenty minutes. Similarly, during the subsidence of a wheal caused by intradermally administered histamine, the site is refractory to an allergen.[20]

This evidence shows that there is one stage of refractoriness to an allergen which is not due to the the inability of the capillary to react to histamine by wheal formation but is probably due to the failure of the allergen to react with the cells to produce an H substance.

Due to Urticariogenic Drugs Other Than Histamine.—Alexander, Elliott and Kirchner[6c] reported some very interesting observations on refractoriness, which are basic. First, they find that refractoriness is a quantitative reaction; i. e., whealing may not occur at one period of recovery from whealing when the previous concentration of drug is used, but may occur in response to a stronger concentration. Second, they find that urticariogenic drugs may be grouped as regards the

17. Alexander, Elliott and Kirchner.[6c] Cooke, R. A.: J. Immunol. **7**:219, 1922.
18. Lewis.[1a] Zurhelle, E.: Dermat. Ztschr. **72**:129, 1935.
19. Shaffer, B.: J. Invest. Dermat. **3**:159, 1940.
20. Hare, R.: Heart **13**:227, 1926.

length of their refractory period. For example, drugs in group A, such as pilocarpine and physostigmine, render the skin unresponsive to a second application of the drug for a longer period (forty-eight hours) than do drugs in group B, such as codeine, morphine and atropine (twelve to twenty-four hours), and drugs in group C, such as histamine (one hour), render the skin unresponsive for a relatively short period. Refractoriness developed in response to pilocarpine and physostigmine is analogous to that developed to an allergen, which fact suggests that these drugs produce H substance only. Codeine, morphine and atropine may produce some H substance and also may act directly on the blood vessels as does histamine, whereas histamine does not release any H substance but acts solely on the blood vessels.

The evidence available on the mechanism of refractoriness to urticariogenic agents shows quite clearly that something other than the production of histamine is involved in most urticarial reactions. Early in the course of recovery from an urticarial reaction the blood vessels are not responsive to histamine; later they are responsive to histamine but not to certain urticariogenic allergens and drugs, and the reason that whealing does not occur apparently is that there is exhaustion of the production of H substance by the cells which react with the allergen.

*Action of Antihistaminic Drugs.*—Antergan® (N,N-dimethyl-N′-phenyl-N′-benzyl-ethylenediamine), neoantergan® (N,N-dimethyl-N′-[p-methoxy-benzyl]-N′-[α-pyridyl]ethylenediamine), diphenhydramine hydrochloride (benadryl hydrochloride®), and tripelennamine hydrochloride (pyribenzamine hydrochloride®) decrease the experimentally induced histamine flare and wheal when the dose of histamine is minimal and the dose of antihistamine drug is maximal.[16] The antihistamine drugs diminish dermographic responses and responses to intradermally administered antigens and benefit a large percentage of patients with acute and chronic urticaria.[16]

Last and Loew [6b] studied the effect of various urticariogenic agents on the permeability to trypan blue of the blood vessels of the skin of the rabbit. They found that diphenhydramine hydrochloride and neoantergan® prevented or diminshed the increased permeability of the dye due to a local injection of histamine. Favorable results were not obtained when trypsin, snake venom, staphylococcus toxin, tetracaine, codeine or horse serum in a sensitized rabbit was used. These negative results may have been due to several causes. First, the dose of the toxic substance may have been too large in relation to the potency of the antihistaminic drug. Second, the increased permeability may have been due to the direct action of the toxic agent on the capillary. Third, an H substance other than histamine may have been produced by the cells. If the first condition exists, a more potent antihistaminic drug is required. If the second does, an agent which will "toughen" or support the capillary

itself is needed. If the third is the case, then anti-H-substances other than antihistaminic compounds will have to be sought.

Antihistaminic drugs may act to decrease the vascular effects of histamine in several ways: (1) by direct action on the vascular endothelium to decrease permeability, (2) by speeding the destruction of histamine or (3) by competing for the cell receptors of histamine. There is no evidence supporting the first two hypotheses. It appears from the evidence that diphenhydramine hydrochloride decreases the action of histamine on blood pressure and intestinal strips by competing for or blocking cell receptors for histamine.[21] This would imply that diphenhydramine hydrochloride decreases the whealing response to histamine by competing for or covering up receptors concerned in rendering the capillaries more permeable. This action would concern the endothelial cells more than the muscle cells of the peripheral blood vessels, a hypothesis indicating that the reason that recovery of the flare in response to histamine occurs before that of whealing is that the endothelial cells of the capillaries are inactivated for a longer time than are the muscle cells and Rouget cells.

### OBSERVATIONS ON SORBITOL MONOLAURATE IN THE DOG

The changes induced by sorbitol monolaurate in the body of the dog resemble those which are associated with peptone and anaphylactic shock, with two definite exceptions. One exception is that when the chemical is injected intravenously (20 to 50 mg.) the fall in blood pressure is less precipitous and the greatest concentration of the vasodepressor substance in the blood plasma is found about ten minutes after the injection. The other exception is that hypercoagulability, rather than hypocoagulability, of the blood occurs after the intravenous injection of the chemical. Refractoriness to the blood pressure–reducing effects of the chemical lasts from four to eighteen hours. A crossed refractoriness between the chemical, peptone and anaphylactic shock is demonstrable. The refractoriness, however, is quantitative and not an "all or none" phenomenon. This evidence may be interpreted as showing that the intravenous injection of the chemical causes the release of two substances: (1) histamine or an H substance and (2) a thromboplastic substance. On the contrary, the vasodepressor and the thromboplastic effects may be due to the same substance.

The foregoing summary is based on experiments too extensive to report here, since this study is primarily concerned with the urticariogenic action of the chemical.

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21. Wells, J. A.; Morris, H. C.; Bull, H. B., and Dragstedt, C. A.: J. Pharmacol. & Exper. Therap. **85**:122, 1945. Halperin, B. N., and Mauris, G.: Compt. rend. Soc. de biol. **140**:440, 1946.

*Urticaria Produced by Sorbitol Monolaurate.*—Urticaria was produced in the course of our studies in more than 200 anesthetized or unanesthetized dogs. Urticaria is quite consistently produced by a dose of 1 cc. of a 1 per cent solution of the chemical given intravenously or by the intradermal injection of 0.01 to 0.04 cc. of a 1:1,000 dilution with an isotonic solution of sodium chloride.

*Relation of the Appearance of Urticaria to the Fall in Blood Pressure.*—In anesthetized animals the fall in blood pressure produced by a dose of 1 cc. of a 1 per cent solution is, as a rule, slight (10 to 30 mm. of mercury), and recovery occurs within thirty minutes. An occasional dog is more sensitive. In both anesthetized and unanesthetized dogs a generalized or patchy flushing of the skin occurs three to five minutes after the intravenous injection of 1 cc. of a 1 per cent solution. This flushing appears at the time the blood pressure starts to fall. The flushing is soon followed by the appearance of typical urticarial wheals (central edema and pallor with peripheral flare). Some of the wheals may become confluent ten to twelve minutes after injection. The wheals begin to disappear after fifteen to twenty minutes and are gone usually in thirty minutes, frequently leaving a slightly reddened patch.

There is a striking relation between the appearance of urticaria and the fall of blood pressure. If the blood pressure in response to the injection of the chemical falls below 80 mm. mercury, urticaria does not occur. In 1 dog 0.8 cc. of a 1 per cent solution of the chemical caused such a pronounced fall in blood pressure that urticaria did not occur. In an occasional dog 1 cc. of a 1 per cent solution causes a slight fall in pressure but not urticaria; in such a case a second injection of 1 cc. has never failed to cause urticaria.

In some instances, thirty to sixty minutes after the urticaria has disappeared with the injection of 0.8 to 1.0 cc. of a 1 per cent solution. urticaria may be induced again, provided some fall in blood pressure is obtained. This procedure may occasionally be repeated as many as three times in the course of five or six hours. In the latter cases, the wheals occur at a new site.

*Refractoriness.*—If a repeated injection of the chemical does not lower the blood pressure, because of refractoriness, then urticaria is not obtained. This fact was observed in many cases and indicates that some vasodilator mechanism is involved. However, in such cases the reddened patch remaining from a previous wheal may become redder. In other words, the animal may become refractory to the mechanism responsible for edema but not to local or generalized flushing. The refractoriness disappears after twenty-four hours. If refractoriness is obtained to a dose of 1 cc. of a 1 per cent solution of the chemical, a larger dose, such as 2.0 or 6.0 cc., unless the blood pressure falls too low, will induce

urticaria. Again, in such a case, the urticaria does not involve the recent former sites of wheals. When the dose of 10 cc. of a 1 per cent solution was reached, the refractoriness was so decided that we could not break through it with larger doses, such as 20 cc., during an experimental period of eight or ten hours.

*Effects on Permeability of Capillaries in Certain Areas.*—If rose bengal is injected intravenously (2 cc. of a 1 per cent solution), two or three minutes after the injection of the chemical—that is, at about the time the blood pressure starts to fall—the urticarial wheal assumes a pink tint. This result shows that this dye, which does not ordinarily stain the skin, filters from the capillaries along with fluid. This method is an excellent way for one to label the location of a crop of wheals. After the wheal is formed, it is not stained by an injection of the dye.

After the disappearance of the wheals, the injection of a second dose of the chemical will cause a flare or reddening of the rose bengal–tinted patches. As already indicated, whealing does not occur in these patches. This reddening is due to vasodilatation. This experiment shows that vasodilatation can occur at the site of a former wheal, but that the site is refractory to formation of edema. This reaction was observed many times.

*Urticaria After Injection of the Chemical Into the Portal Vein.*—Urticaria was as easily produced by making injections (1 cc. of a 1 per cent solution) into the portal vein as by introducing the chemical into the femoral vein. Three experiments were performed. In these experiments the statements made previously relative to refractoriness and formation of a wheal were observed to apply. Thus it may be seen that the liver is not particularly efficient in removing the chemical.

*Urticaria After Evisceration and Hepatectomy.*—The blood pressure of eviscerated-hepatectomized dogs is so sensitive to the chemical that the usual urticaria-producing dose (1 cc. of a 1 per cent solution) produced such a pronounced fall in blood pressure in a number of cases that urticaria could not develop. However, of nineteen experiments, decided urticaria was observed in six and slight to moderate urticaria in nine.

There was no good evidence indicating that absence of the liver sensitized the animals to the urticaria-producing substance, although it certainly sensitized them to the blood pressure-reducing action of the chemical.

*Intra-Arterial Injection of the Chemical and Urticaria.*—It was believed that the urticaria produced by an intravenous injection of the chemical was due to the local action of the chemical either on the endothelium of the capillaries in the skin or on the tissue cells after it had diffused from the capillaries. We believe this hypothesis to be more

likely than the view that the chemical acted on some constituent in the blood, which then acted on the capillaries or tissue cells. The results of the foregoing tests on hepatectomized animals showed that the urticaria-producing substance does not arise from the liver.

Accordingly, 0.3 cc. of a 1 per cent solution of the chemical in an isotonic solution of sodium chloride was injected into the artery supplying the lower legs and abdomen of 4 anesthetized dogs. In each instance, the flushing reaction and urticarial wheals developed only in the skin of the lower abdomen and legs. The carotid blood pressure, however, fell from 10 to 20 mm. of mercury in three to five minutes after the injection.

Two of these dogs, four hours after the first injection, were given 1 cc. of a 1 per cent solution into the femoral vein. The blood pressure fell 10 and 30 mm. of mercury, respectively, and a generalized urticaria appeared. However, the wheals did not appear in the old or former sites on the lower leg and abdomen, but in new sites and to a lesser extent than in the upper part of the body.

*Production of Urticaria by the Intracutaneous Injection of the Chemical.*—This chemical is potent in producing an urticarial wheal with a peripheral flare when injected intracutaneously into a dog. From 0.02 to 0.04 cc. of a 1:1,000 dilution of the chemical in an isotonic solution of sodium chloride causes the production of a large wheal which cannot be distinguished from that caused by histamine. The total dose of sorbitol monolaurate was 0.02 to 0.04 mg.

The formation of the edema fluid is beautifully demonstrated when the intracutaneous injection is made while rose bengal is being injected intravenously.

*Prophylaxis of Sorbitol Monolaurate Urticaria in the Dog.*—Heparin failed to prevent urticaria in five experiments. Epinephrine prevented the development of urticaria due to the chemical and hastens its disappearance. This fact was readily demonstrated in five experiments. Atropine in large doses up to from 4 to 6 mg., given in 1 mg. or 2 mg. doses intravenously, had no effect on the development or disappearance of urticaria in five experiments. Diphenhydramine hydrochloride was used to prevent the wheals in 9 anesthetized dogs and in 11 unanesthetized dogs. In the anesthetized dogs 50 to 100 mg. of diphenhydramine hydrochloride was given intravenously at least five minutes before the administration of the chemical. In only 1 of the 9 dogs were wheals produced, and in this dog they were small and few. It is of interest to note that the general flush of the skin and the flush which occurs in patches were not prevented. This observation indicates that the mechanism responsible for the flushing due to the chemical either is more resistant than the mechanism responsible for the development of a wheal or is different in nature.

In table 1 are shown the results for 11 unanesthetized dogs. It should be emphasized that in the case of these dogs the dose of the chemical was selected by experiment for each dog. Or, for example, if a dose of 1 cc. of a 1 per cent solution caused complete collapse of the dog and urticaria did not occur because the blood pressure was too low, the dose was reduced. That is, if the appropriate dose was used, urticaria always occurred in our experience, and the development of the wheal

TABLE 1.—*Prevention of Monolaurate Urticaria in Dogs by Pretreatment with Diphenhydramine Hydrochloride (Benadryl Hydrochloride®)*

| Dog No. | Wt., Lb. | Sex | Diphenhydramine Hydrochloride* | Dose, Sorbitol Monolaurate (Mg.) | Signs and Symptoms | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Itching | Flush | Redness in Patches | Wheals, Skin | Edema | | Weakness |
| | | | | | | | | | Mouth | Eyelid | |
| 1 | 12.5 | F | Without | 8 | +++ | ++ | +++ | ++ | Edema | Edema | + |
| | | | With | 10 | + | + | ++ | None | None | None | + |
| 2 | 15 | M | Without | 6 | +++ | +++ | ++ | +++ | Edema | Edema | ++ |
| | | | With | 6 | + | + | + | None | None | None | + |
| 3 | 15 | F | Without | 6 | None | +++ | ++ | ++++ | Edema | Edema | None |
| | | | With | 6 | None | + | + | None | None | None | None |
| 4 | 15 | F | Without | 10 | +++ | +++ | ++ | +++ | Edema | Edema | +++ |
| | | | With | 10 | None | + | + | None | None | None | + |
| 5 | 15 | M | Without | 9 | None | +++ | + | ++++ | Edema | None | ++ |
| | | | With | 9 | None | None | None | None | None | None | + |
| 6 | 19 | M | Without | 10 | +++ | +++ | ++ | +++ | None | None | + |
| | | | With | 10 | + | + | + | None | None | None | None |
| 7 | 13 | F | Without | 8 | None | +++ | +++ | +++ | ++ | + | + |
| | | | With | 8 | None | + | + | None | None | None | None |
| 8 | 13 | F | Without | 3 | ++++ | ++++ | ++++ | ++++ | ++++ | ++++ | + |
| | | | With | 3 | None | ++ | +++ | + | ++ | ++ | None |
| 9 | 13 | F | Without | 5 | None | ++ | ++ | +++ | +++ | ++++ | ++ |
| | | | With | 5 | None | None | None | None | None | None | None |
| 10 | 10 | F | Without | 3 | ++++ | +++ | +++ | +++ | ++ | ++ | ++ |
| | | | With | 3 | None | +++ | +++ | + | None | None | ++ |
| 11 | 17 | M | Without | 9 | + | ++ | +++ | +++ | +++ | +++ | None |
| | | | With | 9 | None | + | None | None | None | None | None |

* The total dose was 50 mg., given intravenously. One or two days elapsed between each test on each dog. The sorbitol monolaurate was given five to ten minutes after the diphenhydramine hydrochloride.

was prevented by the appropriate dose of diphenhydramine hydrochloride.

It is entirely possible, however, that cases will be found in which wheal formation will not be entirely prevented. In this connection, it should be noted from the results in table 1 that, although edema or wheal formation was prevented in all dogs studied to date, itching and flushing were variably influenced.

On 5 other dogs we determined the appropriate urticaria-producing dose of sorbitol monolaurate (the interval between injections of this

compound was forty-eight to ninety-six hours) and injected tripelennamine hydrochloride intravenously from fifteen to twenty minutes before the given dose of the monolaurate.

The amount of tripelennamine hydrochloride used on the first 2 dogs was 50 mg., but because it caused severe convulsions we decreased the dose, even though the prevention of urticaria was not very definite in 1 of the 2 dogs receiving 50 mg.

When we injected very slowly 4 mg. per kilogram of body weight of tripelennamine hydrochloride in 2 of 3 dogs, neither edema nor wheals developed and 1 of these 2 dogs and the third one (which had wheals) had slight convulsions.

TABLE 2.—*Prevention of Monolaurate Urticaria in Dogs by Pretreatment with Tripelennamine Hydrochloride (Pyribenzamine Hydrochloride®)*

| Dog No. | Wt., Lb. | Sex | Tripelennamine Hydrochloride | Dose, Sorbitol Monolaurate (Mg.) | Signs and Symptoms | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Itching | Flush | Redness in Patches | Wheals, Skin | Edema | | Wea |
| | | | | | | | | | Mouth | Eyelid | |
| 1 | 19 | M | Without | 10 | ++++ | ++++ | ++++ | ++++ | +++ | ++ | No |
| | | | With (34 mg.) | 10 | +± | ++± | None | +± | + | .... | .... |
| 2 | 15 | F | Without | 8 | +++ | +++ | ++++ | ++++ | ++++ | +++± | ++ |
| | | | With (50 mg.) | 8 | None | +++ | +++ | + | None | None | ++ |
| 3 | 17 | M | Without | 10 | +++ | ++ | ++± | ++ | ++ | + | + |
| | | | With (31 mg.) | 10 | None | None | None | None | None | None | No |
| 4 | 18 | F | Without | 10 | ++± | ++ | ++ | +++ | ++ | + | No |
| | | | With (32 mg.) | 10 | None | None | None | None | None | None | No |
| 5 | 19 | M | Without | 10 | ++++ | +++ | +++ | +++ | +++± | ++++ | ++ |
| | | | With (50 mg.) | 10 | None | ± | + | None | None | None | No |

## A METHOD OF ASSAY OF ANTIURTICARIAL DRUGS

The antiurticarial drugs which are now available—diphenhydramine hydrochloride and tripelennamine hydrochloride—are not so satisfactory as might be desired. Attempts undoubtedly are being made to produce better synthetic compounds.

Since urticaria can be consistently produced in dogs by the appropriate dose of sorbitol monolaurate, this reaction would serve as the basis of an assay for the antiurticarial properties of antihistaminic compounds.

## COMMENT

Clinical urticaria is considered an allergic phenomenon. In the case of sorbitol monolaurate one deals with a pure and relatively simple and potent urticariogenic agent which causes a generalized urticaria when introduced into the circulation of an animal naturally susceptible.

The dog is susceptible, and the cat, rabbit and monkey are not susceptible. Man, as indicated by intradermal tests, does not appear

to be susceptible. Sorbitol monolaurate is not unique in the property of producing a "triple response" on being injected intradermally, since many substances do this; nor is it in doing so when injected intra-arterially, since curare will do the same thing.[22] It is unique in being a pure, rather simple chemical substance which consistently produces a typical urticarial wheal when given intravenously in a dose of a few milligrams.

Wheal formation in the skin is explained as being the result of a special form of cell injury in which histamine or an H substance is produced to cause a local increase in blood flow and capillary permeability. If sorbitol monolaurate releases histamine to cause a wheal, why then does not histamine cause urticaria when given intravenously? It might be replied that when histamine is released in anaphylactic shock the blood pressure falls so low that whealing cannot occur, or that when histamine is given intravenously in a dose adequate to cause urticaria the fall in blood pressure is too great, or that when histamine is given slowly intravenously in amounts adequate to cause flushing of the skin and not cardiovascular collapse the concentration of histamine in the skin is not adequate to cause whealing. On the other hand, sorbitol monolaurate is sufficiently injurious to the capillaries of the skin that sufficient histamine or H substance is released locally to cause urticarial wheals. Such an explanation requires the additional assumption that when the drug is given in urticariogenic doses the skin is more susceptible than other tissues to injury with the monolaurate: The evidence for this assumption is that in such doses no other anatomic lesions are observed, nor are there any apparent physiologic disturbances.

The results of the studies of refractoriness to the monolaurate-induced urticaria, as far as they have extended, show no difference between this urticaria in the dog and that induced by allergens or substances which apparently exhaust the ability of the cells to form an H substance in man. The H substance released by the monolaurate has a histamine-like and thromboplastic action.

## SUMMARY

Knowledge regarding the mechanism of the urticarial reaction is outlined.

The intravenous or intradermal injection of appropriate amounts of sorbitol monolaurate consistently causes urticaria in the dog, but not in the cat, the rabbit or the monkey. The intravenous injection of 8 to 10 mg. in a dog causes urticaria. The intra-arterial injection of 0.3 cc. of a 1 per cent solution causes urticaria in the skin confined to the

22. Grob. D.; Lilienthal, J. L., and Harvey, D. M.: Bull. Johns Hopkins Hosp. **80**:299, 1927.

distribution of the artery. The intradermal injection of 0.02 to 0.04 cc. of a 1:1,000 dilution in an isotonic solution of sodium chloride will cause the formation of a wheal with a surrounding flare in the dog; this reaction does not occur in man.

By labeling the site of previous wheals by injecting a dye, rose bengal, intravenously at the time wheals are forming, we showed that the site of a previous wheal is refractory to the formation of a new wheal for four to eighteen hours.

A study of the refractoriness indicated that the urticarial reaction caused by the monolaurate resembles that caused by allergens.

The evidence indicates that the intravenous injection of the monolaurate releases from the capillary endothelium or the skin in patches a substance or substances having a histamine-like and thromboplastic action.

This monolaurate urticaria is ameliorated by diphenhydramine hydrochloride (benadryl hydrochloride®) and tripelennamine hydrochloride (pyribenzamine hydrochloride®), the wheals being most readily prevented by these antihistaminic drugs.

It is suggested that monolaurate urticaria in dogs may be used for the assay of antiurticariogenic drugs.

# COLLOID MILIUM

HOWARD HAILEY, M.D.*
ATLANTA, GA.

SEVERAL recent reviews of the literature on colloid milium by Robinson and Tasker,[1] Reuter and Becker,[2] Way [3] and others make it inappropriate to include a complete review in this report.

Gilbert and Cox,[4] both of the Australian Army Medical Corps, reported 8 cases of colloid degeneration observed at an Australian general hospital. They stated the belief that sunlight is an important factor in the etiology of this condition.

While the theory was expressed by Anderson,[5] Way and others that a vitamin deficiency may exist and that it may be an etiologic factor in the development of colloid milium, there is not an unanimity of opinion as to the etiology of this condition. In the 2 patients whose cases I report here, the question of vitamin C as an etiologic factor is problematic. Both patients enjoyed good health, and their economic status was better than average.

Subjective symptoms were absent in both patients. The lesions were prevalent on the face, the ears, the sides of the neck and the dorsa of the hands. They were elevated and yellowish red and varied from 1 to 5 mm. in diameter. In some areas the lesions were discrete, while in others they were closely packed together. They were firm and had the feel of lesions of lymphangioma circumscriptum. Puncture of a lesion usually elicited a minute amount of blood.

It was readily seen that the lesions were not true vesicles. Pressure was necessary to empty the contents of the "pseudovesicle" or "bulla." The "pseudobulla" was apparently the result of the confluence of several lesions. The contents of a lesion were granular and gelatinous.

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* Formerly Associate Clinical Professor of Dermatology, Emory University School of Medicine.

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

1. Robinson, S. S., and Tasker, S.: Colloid Degeneration of the Skin, Arch. Dermat. & Syph., **52**:180-181 (Sept.) 1945.

2. Reuter, M. J., and Becker, S. W.: Colloid Degeneration (Collagen Degeneration) of the Skin, Arch. Dermat. & Syph. **46**:695-704 (Nov.) 1942.

3. Way, S. C.: Colloid Milium: A Vitamin Deficiency Disease? Arch. Dermat. & Syph. **45**:1148-1155 (June) 1942.

4. Gilbert, T. M., and Cox, C. B.: Colloid Degeneration of the Skin: Report of Eight Cases, M. J. Australia **2**:21 (July 6) 1946.

5. Anderson, N. P., cited by Way.[3]

Benign cystic epithelioma, hydrocystoma and lymphangioma circumscriptum are the conditions most likely to be confused with colloid milium.

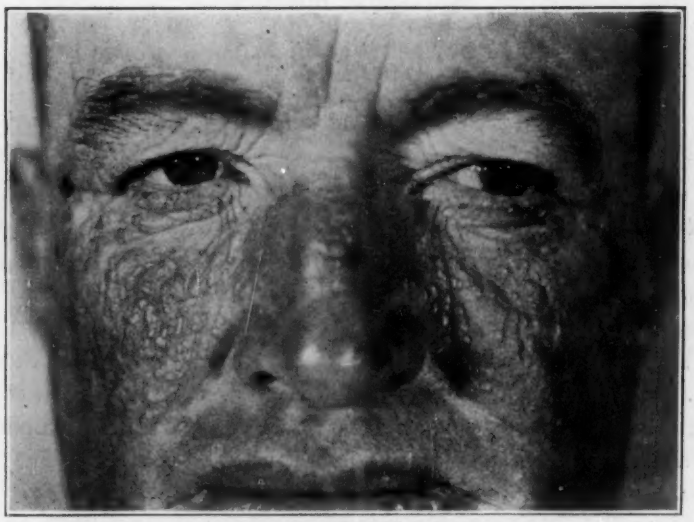

Fig. 1 (case 1).—Appearance of lesions on the face.

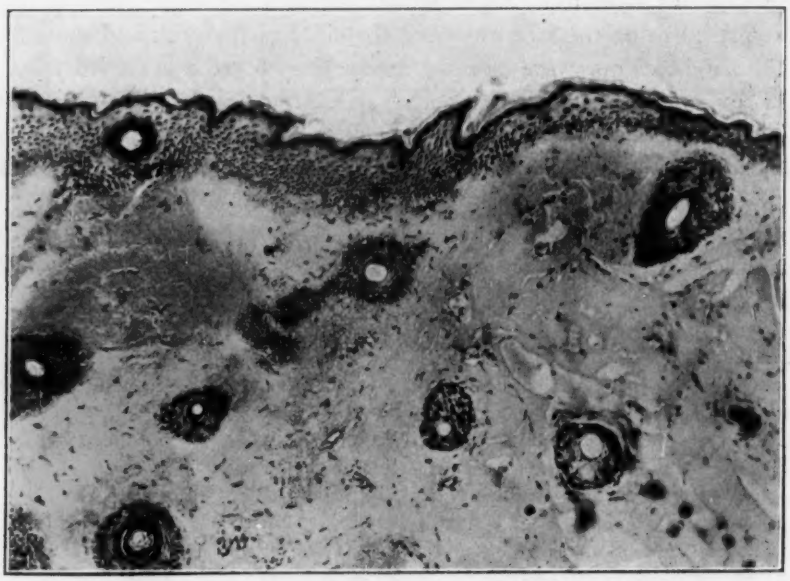

Fig. 2 (case 1).—Section of a lesion; hematoxylin and eosin stain; × 75.

## REPORT OF CASES

Case 1.—T. J. M., a white man aged 39, was first seen by me in December 1946. His occupation was manager of a trucking business, and he estimated that he worked out of doors 50 per cent of his time. His general health was excellent.

He had red hair, brown eyes and a ruddy complexion. His face, ears and the dorsa of the hands presented lesions as previously described, which had begun at the age of 30. Various treatments, including local keratolytic remedies, roentgen irradiation and curettage of small areas, were carried out. Only those areas which were curetted remained free of lesions. On Oct. 30, 1947, treatment was begun with ascorbic acid, 50 mg. three times a day. The patient was last seen by me on March 23, 1948. After five months of medication with ascorbic acid, the condition appeared to have been uninfluenced. The patient said, "Doctor, I can recall that this condition was much worse four or five years ago, and it is worse every summer and gets better in the wintertime".

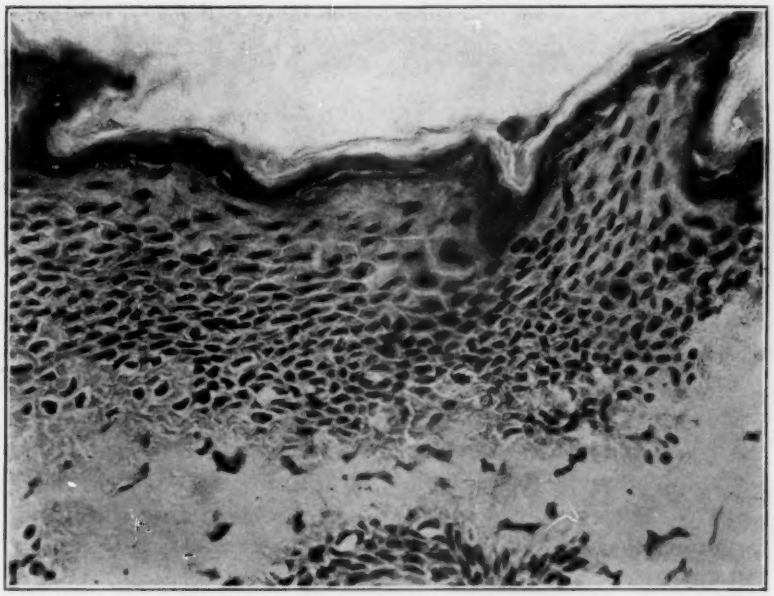

Fig. 3 (case 1).—Section of a lesion; hematoxylin and eosin stain; × 350.

CASE 2.—A. C., a white man aged 40, was first seen by me on Aug. 30, 1945. He operated a farm equipment agency and spent about half his daylight time out of doors. His general health was excellent. His eyes were hazel colored, and he had a ruddy complexion. On his face, the sides of the nose, the ear lobes, the back of the neck and the dorsa of the hands were a large number of elevated, yellowish red lesions, as before described. The patient was seen from Aug. 30, 1945, to Dec. 7, 1946, at fairly regular intervals. The maximum safe dosage of roentgen radiation was administered, without noticeable results. Curettage of areas of the dorsa of the hands produced corresponding smooth atrophic areas. This result apparently displeased the patient. Subsequently, solicitation by mail failed to obtain the patient's cooperation in testing the value of ascorbic acid in treatment of his condition.

## HISTOLOGIC EXAMINATION

The reports by different histopathologists vary in lesser details, but the essential facts are in agreement. The epidermis is thinner than

normal; the rete pegs are absent, and homogeneous masses which represent the degenerative process are found in the upper portion of the derma. There is a tendency for the masses to appear at right angles to the epidermis. The degenerative process affects the walls of the blood vessels.

### TREATMENT

Curettage followed by keratolytic dressings brought about the most satisfactory destruction of the lesions. Roentgen therapy was valueless in both of my patients. Treatment with ascorbic acid for approximately five months failed to improve the lesions in 1 patient. Probably protective measures against sunlight offer the best treatment against this condition.

### SUMMARY AND CONCLUSIONS

Two cases of colloid milium of Wagner are reported.

The disease is probably not as rare as has been previously believed.

In those few cases reported in which administration of ascorbic acid cured the condition or influenced it favorably, the question of coincidence is in order.

The patient in this report who cooperated in experiments with prolonged ascorbic acid medication failed to show improvement. He had noted that the condition improved and regressed without apparent cause, except that he observed that it was worse in the summer.

Geographic location of patients whose cases have been reported appears to influence the incidence of the disease. Where the daily average of hours of sunlight is greatest it seems that this condition is more prevalent.

Results of treatment are unsatisfactory.

Suite 107 Doctors Building, 478 Peachtree Street.

## ABSTRACT OF DISCUSSION

DR. NELSON PAUL ANDERSON, Los Angeles: I am sure that you could not expect anybody from a citrus fruit–growing state to agree with Dr. Hailey's remark concerning the lack of value of ascorbic acid in treatment of this disorder. I believe that everyone has certain preconceived ideas, particularly as regards degenerative diseases. A slide like the one shown today immediately suggests an irreversible change. However, many of these degenerative changes are not irreversible. The answers may not be known now, but the lock is there waiting to be opened by the right key. Whatever the causative factors may be in this disease and in other so-called degenerative diseases, if we take the viewpoint that these are irreversible degenerative diseases about which nothing can be done, then we will not be on the lookout for new therapeutic ideas which might be of benefit. I would like to point out that this was the situation in Way's case in which there was a return of the skin to normal, and in Robinson's case, in which there was also a return to a normal condition. Along this same

line of thought there is the presentation of Burgess, of a case of necrobiosis diabeticorum in which there was a return to normal. In lichen sclerosis et atrophicus I have seen astounding reverses to normal with the local application of estrogenic cream in women who had several hundred lesions scattered all over the body and genitalia. One positive result in a disease where all previous attempts have been negative is worth a great deal more than all the negative results that are obtained. I have little doubt as to the value of ascorbic acid in treatment of colloid degeneration of the skin. Even with the daily administration of 500 cc. of ascorbic acid by mouth, Robinson could raise the blood level only to 0.8 mg. per hundred cubic centimeters. Improvement was noted two months after the beginning of this therapy. The fact that people are in certain so-called higher economic groups means nothing in regard to adequacy of diet. Finally, I should like to mention that, in a number of cases of colloid degeneration, hypercholesteremia occurs. This condition might be the result of an effect of the adrenal gland on the thyroid gland.

Dr. John Belisario, Sydney, Australia: I was interested to hear Dr. Hailey's paper and Dr. Anderson's discussion. Although this disease is rare, in Australia it is seen every now and again. Furthermore, I would like to mention that this condition is more frequent in fair-skinned blonds who are out in the sunlight a good deal. I saw more of it in New Guinea than is usual in Australia. The reason is probably that the people in New Guinea had their hands exposed to strong sunlight all day. With regard to treatment, I have not been successful with the use of ascorbic acid. I have used it in large doses but have seen no improvement. Some of my colleagues told me that they had seen improvement under this treatment. I have seen 1 or 2 cases clear up independently. I have used roentgen irradiation but the only thing that has given complete regression has been electrodesiccation or curettage.

Dr. Hailey, Atlanta, Ga.: I wish to thank Drs. Anderson and Belisario for their discussions. I was especially interested in hearing Dr. Belisario state that colloid milium was not a common condition but was more frequent in some geographic areas than others.

Colored pictures were made before the treatment with ascorbic acid and after treatment. Through the use of a hand lens I was unable to note any diminution in the number of lesions.

# CALCIFEROL IN THE TREATMENT OF CUTANEOUS TUBERCULOSIS

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With the Collaboration of John R. Haserick, M.D.
MINNEAPOLIS

VITAMIN D therapy has been used in cutaneous tuberculosis by a large number of clinicians in many countries since the first reports of Charpy and Dowling extolled the value of calciferol (vitamin $D_2$) in the treatment of lupus vulgaris. That the method has real value is proved beyond a doubt, but there are still some unanswered questions about the action and use of this potent vitamin; therefore, a review of our experience and of that of others up to the present time seems in order.

In using calciferol in the treatment of cutaneous tuberculosis at the University of Minnesota Hospitals, the French and English methods of administration have been combined. We prefer Dowling and Thomas' adjustment of daily doses to each patient. Our rule has been to give, orally, 1,000 units per kilogram of body weight per day to the bedridden patient and up to 2,000 units per kilogram to the ambulatory patient. It is interesting to note that despite this attempt to prevent reactions by halving the dose for bedridden patients, they were the very patients who had the largest number of toxic reactions.

Charpy recommended and has continued, to the time of writing, to prefer alcohol as the vehicle for the crystallized vitamin $D_2$. He stated the belief that calciferol in oil did not give consistent results. Mayoux stated that vitamin D in oil was consistently ineffective. Charpy [1] stated recently that when no improvement occurs by the fifteenth day of administration, failure of absorption or failure of tissue permeability owing to the presence of too much salt in the tissues must be suspected. He did not state how the presence of these conditions could be established.

At first viosterol in oil was used, because it was available; later a solution of calciferol in propylene glycol (drisdol®),[2] especially

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From the Division of Dermatology, University of Minnesota, Henry E. Michelson, Director.

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

1. Charpy, M. J.: Vitamin D in Cutaneous Tuberculosis, Lancet **2**:398, 1947.

2. The drisdol® used in this study was furnished by the Winthrop Chemical Company.

prepared in a concentrated form of 50,000 units per cubic centimeter, was used. The results varied with either solvent, and we cannot state that either is superior or that fewer reactions are encountered with the one or the other. The advantage of propylene glycol as a solvent is that, being water miscible, it is injectable. This property is being utilized in inhalation experiments now under way in cases of pulmonary tuberculosis; when the substance is vaporized, it can be utilized without danger of lipid pneumonia.

We have now treated 25 patients with cutaneous tuberculosis with calciferol. The series comprises 7 patients with lupus vulgaris, 9 with erythema induratum, 4 with papulonecrotic tuberculids and 5 with colliquative tuberculosis.

### LUPUS VULGARIS

Since the results of treatment with calciferol are especially striking and successful in lupus vulgaris, one must analyze this particular form of tuberculosis in order to find, if possible, an explanation for the curative susceptibility of the disorder to large doses of the vitamin.

The disease has a definite geographic distribution outside the United States; although occasional patients with lupus vulgaris are seen here, most of them are not native born but come from areas where the disease is endemic. In addition, patients with lupus vulgaris come from a stratum of society which often means restricted purchasing power and, hence, an inadequate diet, frequently with severe deficiency of the foods that contain vitamin D; there has been prenatal deprivation, both calorically and in vitamin content. Neumann has stated that in pulmonary tuberculosis, a normal daily diet of 40 calories per kilogram of body weight was desirable, with an acceptable mixture of foods; this standard is rarely encountered in those areas of Western Europe where lupus vulgaris is so common. The relation of vitamin D to sunlight is well known; the studies of Marchionini [3] demonstrated the absence of lupus vulgaris in those parts of the world where the number of days per year with bright sunlight is high.

Although nutrition and climate both play a prominent role in susceptibility to lupus vulgaris, climate seems the more important. The incidence of lupus vulgaris in different climates shows that moist, cool areas, poor in sunlight, favor development of the disease. In Europe it is much more frequent in the north than it is near the Mediterranean. In fact, the incidence declines from north to south, and the disease is practically nonexistent near the Equator. Marchionini cites many well known observers on this point; for example, Pautrier's patients in Strasbourg came largely from the valleys of

3. Marchionini, A.: Die Hauttuberkulose in Anatolien, Arch f. Dermat. u. Syph. **185**:363, 1944.

the Vosges, a relatively moist and cool region. In Germany, Stumpke called attention to the great number of patients from the western and southwestern areas near Switzerland (where Miescher had noted that his patients came largely from the peasant class) and emphasized the poor economic level as well as the scarcity of sunlight in the areas of the country where lupus was most frequent. Gron reported that 60 cases of lupus vulgaris had been reported in Bergen, as against 18 for the same period in Stockholm. It is interesting to note that in northern Italy, cutaneous tuberculosis accounts for 6.75 per cent of all cases of cutaneous diseases, whereas in Rome, the percentage drops to 1.07 and in Naples, to 0.8. The only figures available to us for the United States were furnished by Buckley, by Duhring and by Pusey. All three investigators stated individually that the incidence of lupus vulgaris in the dermatologic clinics where they tabulated reports of cutaneous diseases was 0.3 per cent.

*Incidence of Cutaneous Tuberculosis in Relation to all Cutaneous Diseases*

| | Oslo (Danbolt), % | United States (Spitzer), % | Ankara (Marchionini), % |
|---|---|---|---|
| Cutaneous tuberculosis, Total | 3.76 | 0.818 | 0.53 |
| Tuberculosis luposa | 1.5 | 0.3 | 0.18 |
| Tuberculosis colliquativa | 0.45 | 0.2 | 0.34 |
| Tuberculosis indurativa | 0.41 | 0.01 | 0.002 |
| Tuberculosis ulcerosa | 0.45 | ... | 0.004 |
| Tuberculosis verrucosa | 0.06 | 0.3 | 0.002 |
| Tuberculosis papulonecrotica | 0.019 | ... | ..... |
| Tuberculosis lichenoides | .... | 0.008 | ..... |

Marchionini studied tuberculosis of the skin in Turkey, where, in contrast to western Europe, the total number of cases of cutaneous tuberculosis was only 0.53 per cent and that of lupus vulgaris only 0.18 per cent of all recorded cases of cutaneous disease. An interesting comparison of the frequency of various types of cutaneous tuberculosis in northern Europe and in the United States with the frequency of the same types in Turkey is afforded by the table.

The striking contrast occurs in the frequency of lupus. Obviously Danbolt's and Marchionini's figures are more reliable, for they were taken from their own clinics in one locality, whereas Spitzer's were calculated from the meager American statistics available. The total percentage of lupus in Oslo is much greater than that in either the United States or Ankara, and the percentage in Ankara is much the lowest of the three figures quoted.

Without delving further into the geographic and climatic factors that favor the development of lupus vulgaris, one may readily conclude that sunlight must play a decided role, but there are some exceptions which turn one's attention to diet. Trubitsch found no lupus vulgaris in the Eskimos of western Greenland, while Olin found the percentage in Finland to be about the same as in other parts of western Europe,

in spite of the high mortality rate for pulmonary tuberculosis in Finland; these data may be contrasted with those for Japan, where the incidence of pulmonary tuberculosis is also extremely high, but where there is practically no lupus vulgaris. In China, Richter found cutaneous tuberculosis to be less frequent than in northern Europe, but present to an appreciable degree. One must therefore investigate, if possible, the social, environmental and nutritional factors, a procedure which offers many difficulties.

Von Mallinckrodt-Haupt called attention to the unhygienic environment of patients with lupus vulgaris in the Eifel district of Germany: their general poverty, their dwellings with dark, unventilated rooms, their lack of bathing facilities, and their diet of potatoes and cereals, low in vitamins. These factors, combined with the small number of hours of sunlight per year, make for conditions which we consider favorable for the development of lupus vulgaris, particularly when one keeps in mind the ever present infective sources, both human and bovine, in backward areas. Although these factors do not entirely explain all lupus vulgaris cases, a sun-poor, cold climate, together with an inadequate diet, seems to dispose to the development of lupus vulgaris much more than does an inadequate diet in a sunny, warm climate.

Surely patients with such a disease are fit subjects for a therapeutic regimen which includes improved general nutrition; possibly vitamin D in massive doses in some way rectifies the main deficiency or repairs damage done when the patient was under less favorable dietetic influences.

Before the advent of vitamin D therapy in lupus vulgaris. the most successful treatment of that disease was the Finsen form of ultraviolet therapy. According to Lomholt, this form of treatment, combined with a general antituberculosis regimen, gave promise of about 80 per cent success, especially when begun at the first appearance of the disease. Just as today one may ask why vitamin D brings about improvement in cases of lupus vulgaris, so did the advocates of the Finsen treatment try to find the reason for its beneficial action. Obviously the first thought concerned the effect on the tubercle bacillus, but it was soon demonstrated that the chemical rays of the Finsen light penetrated to only about 0.1 mm. and below this were entirely lost, so bactericidal action could not have been the reason for the healing action. Most observers finally came to the conclusion that since healing under Finsen treatment brought about scarring, what actually took place was the production of an intense tissue reaction. This process began with an active hyperemia, with dilatation and thrombosis of the superficial and even of deeper vessels, and was followed with edema and cellular infiltration, resulting in vacuolation and necrosis of the epithelium and often in necrosis of the lupous

tissue, with crusting and subsequent formation of fibrous tissue. Healing often was incomplete; areas of lupous tissue found in the scar had to be dealt with. It was noticed that patients who lived at Finsen institutes made more progress than those who lived at home and only attended for irradiation. When the Gerson salt-free diet was introduced, it was also observed that the Gerson diet plus the Finsen treatment was superior to either alone.

Throughout the history of successful therapy for lupus, nutritional and hygienic factors have played an important part. Now the success of vitamin therapy seems to throw some light on the reason. Vitamin D is produced and found in the skin. Ultraviolet radiation is important in the production of vitamin D. The lupus vulgaris patient must have, or lack, certain qualities of the tissues which make him susceptible to this form of tuberculous inflammation. Evidently, when his skin becomes suffused with vitamin D, a reaction takes place similar to that produced by the Finsen treatment. Healing is apparently brought about in the same manner in both forms of treatment. It seems fair to presume that there is a common factor, and that Finsen therapy was probably successful because of the local production of vitamin D. The interrelation of the various vitamins is well known; hence, a diet rich in several vitamins may have assisted such action in Finsen therapy. The reports of combined Finsen and vitamin D therapy are very good, but much time and observation are needed in order to evaluate any procedure in so resistant, chronic and recurrent a disease as lupus vulgaris.

Charpy, Dowling, Lomholt and others are in accord about dosage, duration of treatment, percentage of improvement and other factors in the treatment of lupus vulgaris. They agree that most patients tolerate large doses of vitamin D and that the best effects are produced at almost a level of overdosage; Dowling stated that the total dose in his cases ranged from 9,500,000 to 62,500,000 units in adults and from 4,500,000 to 33,500,000 units in children. These writers also agree that the treatment must be carried on at reduced dosage for as long as a year. In successful cases there is no doubt about clinical cure; the anatomic cure is doubtful.

In ascertaining the value of treatment with calciferol in lupus vulgaris, in addition to our own observations, we have carefully examined the literature which has accumulated over the past five years and have been fortunate in receiving valuable personal communications from Dr. D. E. Macrae of England and Dr. G. Miescher of Switzerland. The experiences of almost all those who have worked with calciferol are much alike. There are some small variations, but the general uniformity of the results speaks for the success of the method.

It may be stated unequivocally that calciferol is of great value in the treatment of lupus vulgaris. It is not a specific, but it acts more

favorably in lupus vulgaris than in any other form of cutaneous tuberculosis in which it has been tried. The importance of familiarity with the rate of progress of the disease, variation in dosage with the vitamin, combination of the treatment with physical therapy, the all important time element, and many other details can be appreciated only when they are dealt with. Regulation of the dose to suit the patient must be emphasized. Although 100,000 to 150,000 units per day (1,000 to 2,000 units per kilogram of body weight) is the usual dose employed, we have found it advantageous to reduce the dose to as low as 10,000 units daily for the patient who is somewhat intolerant of calciferol.

Progress under calciferol therapy is by no means uniform in all cases. There is a decided variation, both in the time required for response and in the rate of improvement. There may be an initial period of lack of response, or even of increase in the inflammatory appearance, but if the dose is made tolerable and the treatment persevered in, improvement is indicated by a flattening of the plaques, a dulling of the color and, soon, the appearance of white areas between the lupous tissues. Gradually, these areas, which are composed of scars, increase, and fewer and fewer lupous nodules can be seen. Complete clinical scarring may result, but in our series we have not as yet encountered a case in which we were confident from the macroscopic appearance that there was no pathologic activity left.

Microscopic examination of treated areas has revealed tuberculoid structure. In an instance of slow healing a change in the type of structure found was in accord with an observation of Miescher's, that results of histologic examinations made within a few months after the beginning of treatment indicated a tendency for the frank tuberculoid structure to change to a sarcoidal one. This variation may be significant and may even throw some light on the etiology of sarcoidosis, but it cannot be discussed here. All observers have been dismayed at the presence of traces of tuberculous tissue in the areas which apparently were completely healed under calciferol treatment.

In America, one does not often encounter a patient with the severe, destructive and ulcerating lesions seen in Europe; hence, we cannot state which forms of lupus respond best to calciferol therapy. Macrae has tabulated his impressions in that regard. It is our conviction, however, that the more severe and extensive the disease, the longer the treatment must be carried out, and that sustained treatment, even though the dose is much reduced, is better than stopping the treatment completely and then starting it again.

We have not encountered any effects on pulmonary lesions, the presence of which had been determined historically or roentgenologically, nor have we seen the production of pulmonary lesions not previously suspected. The latter result has, however, been reported and

must be kept in mind. Not only pulmonary tuberculosis but also renal tuberculosis has become manifest or developed during calciferol therapy.

A combination of treatment with various physical devices, such as the Kromayer lamp or the Finsen light, or of cautery or application of chemical pastes, with administration of calciferol is entirely feasible and beneficial but fortunately is not often needed. Injections of streptomycin combined with or interspersed with administration of calciferol are indicated, we believe, in a case in which the lesions are resistant or in which progress has come to a standstill. Our experience with such a case is limited to a single instance, in which healing was not at all satisfactory until streptomycin was added; then scarring began and progressed favorably. For this patient the dose of calciferol was reduced to 25,000 units daily, because of some signs of intolerance. Our experience is too small to advise reducing the dose of calciferol when giving streptomycin, but it is a point worthy of consideration.

The addition of calcium is now considered unnecessary when patients are ingesting an average diet. Only those patients deprived of calcium-containing foods need supplemental calcium.

### OTHER DISEASES

*Papulonecrotic Tuberculid.*—One case of papulonecrotic tuberculid of the face responded well in two weeks' time, but after six weeks of therapy the serum calcium rose to 15 mg. per hundred cubic centimeters and the calciferol was discontinued. There was no recurrence of the disease in several months. On the other hand, treatment with calciferol produced no change in the condition of a woman of 24 with papulonecrotic tuberculid, even after five months of treatment. It is of interest that in this case the amount of calcium in the serum and urine was within the normal range after four months of treatment. A patient with extensive papulonecrotic tuberculid involving both legs and arms had had the lesions for six years. There were recurrences and increasingly severe involvement each winter. Under continued calciferol treatment the number of lesions decreased and the seasonal exacerbations were lessened, but lesions still persisted.

Vitamin D therapy in our few cases of papulonecrotic tuberculid has not been successful. In so-called rosacea-like tuberculid we also have seen no striking effect.

*Tuberculous Adenitis.*—Calciferol was used in 5 cases of tuberculous adenitis, including 1 of colliquative tuberculosis. No local change was noted in 3. In the other 2, a severe local reaction occurred, consisting of pain, swelling, fluctuation and drainage of the glands during the second week of treatment. Addison's disease developed in 1 of the latter patients while he was being given calciferol. The second patient improved after the initial softening and drainage of the nodes;

she herself requested that therapy be resumed because of a feeling of well-being she had while taking calciferol.

Macrae, of the Morland Clinics, in England, wrote one of us (H. E. M.) that he has administered vitamin D in from 30 to 40 cases of tuberculous adenitis. He noted a flare-up, similar to the Herxheimer reaction, especially in children; however, after a month or six weeks of increased swelling with breaking down and pus formation, or with increased discharge from sinuses, noticeable improvement took place:

> The benefits of calciferol have shown themselves strongly in several ways. Firstly, in the acute flare-up nodes hitherto unsuspected have sometimes shown themselves, so that more complete eradication of the disease can be carried out. I feel it is these small nodes, containing a few tubercle bacilli and not spotted in the ordinary course of events, that lead to a recurrence of the trouble months or even years afterward.
>
> Operation is surprisingly easy compared with the difficulties of the old days. The most striking feature has been the disappearance of matting and periadenitis. The nodes can be firmly gripped without their bursting and discharging tuberculous pus in the wound, and I have found that after periods of treatment varying from two to nine months, the nodes resemble sebaceous cysts in the ease with which they can be removed.
>
> Roentgenograms of the neck have shown a considerable increase in calcification, and sections of the lymph nodes after removal have shown a very large proportion of calcium deposits, particularly in the center of the node; in some, no lymph node can be seen. In others, a small rim of tuberculous tissue has been found at the periphery. I feel surgical operation is still an essential part of the treatment.

Dr. Macrae unhesitatingly states that calciferol is of very great help, and that although it cannot be regarded as curative, treatment is speeded up and results are pleasing in tuberculous adenitis. As has been stated, our experience is not large. In 1 case, after progress had come to a standstill with calciferol, streptomycin was given; rather striking improvement, scarring and arrest (perhaps cure) of the process resulted.

*Erythema Induratum.*—Erythema induratum has not been affected remarkably under calciferol therapy. We believe that the patient should be given the benefit of a three months' trial. If no improvement has taken place in that period, it is doubtful whether further benefit can be expected. Since circulatory factors are important in erythema induratum, the ideal trial should be combined with bed rest. Under such a regimen we had fair success in 1 case, but as soon as the patient became ambulatory the lesions recurred.

### TOXIC REACTIONS

In our experience, the systemic toxic symptoms and signs were minimal in the group of 25 ambulatory patients. As a precautionary measure, calciferol was not administered to any patient with arteriosclerosis or with impaired renal function. When toxicity occurred, the earliest sign was nausea, with anorexia and headache the next

most frequent. In no case in which the patient was ambulatory was it necessary to stop administration of the drug because of toxic symptoms, though a rapid onset of hypercalcemia (the level for serum calcium was 15 mg. per hundred cubic centimeters) in 1 case prompted us to withdraw it.

Of the 8 bedridden patients, 5 had reactions considered severe enough to discontinue the drug, in spite of reduction (for 4 of them) to one-half the amount of calciferol per kilogram given to the ambulatory patients. Abdominal pain was severe in 2 patients. There was no adequate explanation for the pain except the one, favored particularly in England, that vitamin D liberates lead from the bones and, when the mobilization is rapid, produces the nausea, vomiting and abdominal pain of lead poisoning. Examination of the excretions for lead was not carried out in any of our cases.

Even after the drug was discontinued, hypercalcemia and toxic symptoms persisted for two months in 3 of the 5 bedridden patients. In our experience toxic symptoms did not develop in any patient without hypercalcemia, though hypercalcemia developed in several without toxicity.

Though we had expected systemic toxic reactions to massive doses of calciferol, we were unprepared for the severe local Herxheimer-like reactions in tuberculous adenitis. These usually occurred during the second or third week of therapy and consisted of increased redness, pain and softening of the lymph nodes with copious drainage, and of increase in the area of involvement. When observed over a longer period of time, the local reaction usually subsided and continued improvement then seemed to begin.

In the case of tuberculous adenitis in which Addison's disease developed, with crisis during the second week of calciferol treatment, it is noteworthy that a severe local reaction took place at the site of the subcutaneous adenitis followed with fluctuation and drainage. It is plausible to assume that a similar local reaction may have occurred in the adrenal glands, resulting in the crisis of Addison's disease.

## MODE OF ACTION

There has been no satisfactory explanation for the success of calciferol in the treatment of lupus vulgaris. A hypothesis based on the well known effects of vitamin D does not adequately explain either the clinical response or the pathologic findings. Nevertheless, several factors involved are applicable to physiology and pathology of the skin.

*Effect of Vitamin D on Mineral Metabolism.*—The theory first suggested to explain the effect of calciferol in lupus vulgaris was the natural one that healing was related to the hypercalcemia produced by calciferol. However, both Charpy and Dowling reported patients who responded well with no change in the serum calcium, while other

patients with hypercalcemia did not show a clinical response. Moreover, in post-treatment biopsy in Charpy's cases studied by Vachon and Feroldi,[4] as well as in those of our own small series, there was no evidence of deposition of calcium in or around the tuberculous tissue.

In our cases high blood calcium was a common finding, the level often reaching 16 mg. per hundred cubic centimeters. The rise usually was preceded by an increase of calcium in the urine, the level of which rose from a normal quantitative value (Sulkowitch test) of below 100 mg. per hundred cubic centimeters to as high as 800 mg. per hundred cubic centimeters. It was noted that acidity of the urine was necessary to maintain a direct relation between the level of serum calcium and that of urinary calcium. For 1 dehydrated patient with alkaline urine, the quantitative value (Sulkowitch test) was 89 mg. per hundred cubic centimeters, while the serum calcium persisted at 15 mg. per hundred cubic centimeters after calciferol was discontinued. With restoration of the fluid balance to normal and acidification of the urine with nitrohydrochloric acid, the urinary calcium excretion rose to 878 mg. per hundred cubic centimeters, followed with a rapid drop in the serum calcium.

No change in the serum phosphorus was noted after administration of calciferol. However, the alkaline phosphatase rose late in 3 cases, from normal pretreatment values of 2.2, 1.8 and 1.4 King-Armstrong units to 46, 22 and 18 King-Armstrong units, respectively. In each case, the value returned to normal after the drug was discontinued. These data are in contradistinction to the unchanged or decreased phosphatase values reported by Reed when massive doses of vitamin D were given to arthritic persons, and to the se.ere decrease in serum phosphatase observed by Hansen, McQuarrie and Zigler in 4 cases of osteogenesis imperfecta in which values for blood phosphatase had been normal before treatment. At best, however, the changes in the level of phosphatase would seem to be a secondary factor; they are difficult to correlate with the therapeutic results in cutaneous tuberculosis.

*Direct Effect on the Tubercle Bacillus.*—Attempts to determine the bactericidal action of vitamin D have resulted in contradictory findings. Steenken and Baldwin,[5] in 1937, found no in vitro evidence of a bactericidal effect on cultures of the tubercle bacillus. On the other hand, in 1946, Raab [6] reported that a complete absence of growth of tubercle

4. Vachon, R., and Feroldi, J.: Le traitement du lupus tuberculeux par la méthode de Charpy: Les résultats anatomiques, Ann. de dermat. et syph. **5**:241, 1945.

5. Steenken, W., and Baldwin, E. R.: The Effect of Irradiated Milk Compared with Vitamin D Oils on Inhalation Tuberculosis of Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **37**:348, 1937.

6. Raab, W.: Vitamin D—Its Bactericidal Action, Dis. of Chest **12**:409, 1946.

bacilli had resulted when calciferol was given in propylene glycol, but that no change had occurred when propylene glycol alone was given. Dr. Robert Patnode,[7] of the Department of Bacteriology, University of Minnesota, repeated these important experiments but found that the calciferol in propylene glycol had no more bactericidal effect than did the propylene glycol, which he used as a control.

Most authorities who support the theory of direct action on the bacillus call attention to the local reaction, which has frequently been noted soon after treatment was started. It has been likened to the Herxheimer reaction after antisyphilitic treatment and seems to be limited to cutaneous tuberculosis among all the diseases treated with vitamin D. It was the most common reaction in our cases of tuberculous adenitis and colliquative tuberculosis and was often severe enough to necessitate discontinuing the treatment. Miescher stated that tubercle bacilli could still be identified in the secretion from the lesions of a patient with colliquative tuberculosis, who had been under treatment with vitamin D for over one year.

*Calorigenic Effect of Vitamin D.*—Seel [8] observed that the basal metabolic rate was lowered in rickets, and that vitamin D restored it to normal. Reed,[8] in 1934, found that the drug produced an increased calorigenic effect when given in subtoxic doses to normal rats. Steck, Miller and Reed [9] found that "para-thor-mone" had no calorigenic effect. This information led to experiments on dogs by Deutsch, Reed and Struck,[10] who found that vitamin D no longer had its calorigenic action after thyroidectomy. Bartoli, Feldman and Barnes [8] removed the pituitary gland from dogs and still found no calorigenic response to vitamin D. Thus it would seem that the preparation exercises a calorigenic effect, but mainly through the thyrotropic control of the anterior pituitary gland.

The relation between tissue oxygen consumption and vitamin D intake was studied by two investigators. Presnall,[11] in 1937, found that the "oxygen uptake of the skins of rats on a vitamin D–deficient

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7. Patnode, R.: Personal communication to the author.

8. Cited by Reed, C. I.; Struck, H. C., and Steck, I. E.: Vitamin D: Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations, Chicago University Monographs in Medicine, Chicago, University of Chicago Press, 1939.

9. Steck, I. E.; Miller, D. C., and Reed, C. I.: The Effect of Parathormone on Basal Metabolism of Normal Dogs, Am. J. Physiol. **110**:1, 1934.

10. Deutsch, H.; Reed, C. I., and Struck, H. C.: The Rôle of the Thyroid in the Calorigenic Action of Vitamin D, Am. J. Physiol. **117**:1, 1936.

11. Presnall, A. K.: The Relation of Vitamin D to Skin Respiration, J. Biol. Chem. **121**:5, 1937.

diet was only 50-70 per cent of control rats." Gelfan,[12] in 1935, studied the effect of viosterol on frog muscle. He found that the vitamin D increased the mean oxygen consumption as much as 29 per cent over that of normal controls, which was "analogous to the increased respiration of tissue from thyroid-treated animals."

Clinically, hyperthyroidism frequently is associated with a negative calcium balance, and occasionally results in osteoporosis. Both vitamin D and "para-thor-mone" have been found to correct this negative balance, but what the clinical relation is between hyperthyroidism or hypothyroidism and lupus vulgaris or other forms of cutaneous tuberculosis is not clear. It is noteworthy that Feeny and his associates [13] recently reported a case of "moderate hyperthyroidism" in which the patient had had lupus vulgaris for twenty years, and in which it did not respond after five months of treatment with calciferol. Thus, there are three possible bases for the action of calciferol in cutaneous tuberculosis: the hypercalcemia, the direct effect on the bacillus and the improved metabolism, none of which seems adequate in itself. Since the histologic change in tissue in the lesions of lupus vulgaris after treatment with calciferol is mainly an increase in fibrous tissue and not a deposition of calcium, the action of the vitamin would seem to be due more to an improvement in tissue metabolism than to a change in the mineral constituents. A direct effect on the bacillus in vivo cannot be ruled out, but seems a remote possibility in view of the experiments in vitro.

One may speculate that the dermatologic effect of calciferol is to bring about an activation of devitalized tissue, thus upsetting the static and prolonged balance between the resistance of the host and the weakly invasive powers of the bacillus. With increased oxygen consumption of the individual tissue cells, a proliferation occurs which literally suffocates the enclosed tuberculous structure. The immediate reaction is an inflammatory one, which eventuates in the formation of scar tissue.

*Distribution of Vitamin D in the Body.*—Investigators using calciferol in treatment of other forms of tuberculosis are aware of the distribution of the drug in the body. In 1939, Vollmer [14] administered massive doses of vitamin D to a dying infant three days before death. Postmortem bioassays of the various organs revealed that the major portion of the vitamin D was stored in the skin, brain and liver. No

12. Gelfan, S.: The Effect of Viosterol upon Oxygen Consumption of Frog's Muscle, Am. J. Physiol. **113**:464, 1935.

13. Feeny, P. J.; Sandiland, E. L., and Franklin, L. M.: Calciferol in Tuberculosis: Review of One Hundred and Fifty Cases of Lupus Vulgaris; Review of Twenty-One Cases of Pulmonary Tuberculosis, Lancet **1**:438, 1947.

14. Vollmer, H.: Distribution of Vitamin D in the Body After Administration of Massive Doses, Am. J. Dis. Child. **57**:343 (Feb.) 1939.

appreciable amounts were found in the lungs, spleen or bones. Windorfer [15] reported a similar experiment in 1938, with similar results. Thus no improvement could be expected in pulmonary tuberculosis unless, perhaps, the calciferol were utilized in a form suitable for inhalation.

## COMMENT

The treatment of cutaneous tuberculosis, and in particular of lupus vulgaris, has been greatly advanced by the use of calciferol, and the drug may be safely recommended. One need not have any particular experience with its use in order to give the method a trial. A careful evaluation of the patient's condition, however, is essential. Knowledge of the state of the lungs, an estimate of renal function and a careful evaluation of the general physical condition are all that is necessary in order to proceed with relative safety. Patients receiving calciferol should be seen often, at least once a week, and should be instructed to stop taking the vitamin at once if nausea, anorexia, giddiness or other unusual symptoms develop. Patients with large areas of involvement or with tuberculous adenitis, or those unable to tolerate the usual dosage, should only be treated in the hospital.

The one tuberculous cutaneous condition which warrants prolonged trial and adjustment of dosage to enforce tolerance is lupus vulgaris. The results in the other forms of cutaneous tuberculosis have not been striking enough to justify any risk being taken in order to continue the treatment in the presence of mild signs of intolerance, or to justify continuation of the treatment for periods longer than three months when no improvement is noted.

The treatment of lupus vulgaris is of great economic and social importance. Calciferol therapy is a definite advance over the best that could have been expected of the Finsen treatment. It has shortened the period of treatment, has saved the patient much loss of time and has made him independent, to some degree, of strict supervision and tedious routine. The treatment can usually be carried out without the patient's changing his residence or becoming an inmate of an institute.

If the calciferol treatment of lupus vulgaris is a great help in areas where the disease is endemic, it is an even greater help to dermatologists in this country. Here we have no Finsen institutes; formerly, when lupus vulgaris was encountered, treatment was haphazard at best, because the highly technical facilities and knowledge necessary to carry out even a modified Finsen treatment were lacking. With the advent of calciferol therapy, a reasonably successful and safe treatment for lupus vulgaris is available. The method of its use, the dangers and

15. Windorfer, A.: Ueber die Vitamin-D-Resorption bei Verabreichung hoher Dosen C Vitamin D-Stoss, Klin. Wchnschr. **17**:228, 1938.

the therapeutic possibilities can easily be learned. Since the method is not a specific and may not actually cure lupus vulgaris, further search for therapeutic combinations and improvements in its use is urged.

## SUMMARY AND CONCLUSIONS

A series of 25 cases of cutaneous tuberculosis treated with massive doses of calciferol (vitamin $D_2$) is reported.

From the results and experience obtained, the following conclusions are drawn:

1. Calciferol is a valuable adjunct in the treatment of cutaneous and nodular tuberculosis.

2. It has exceptional value in the treatment of lupus vulgaris.

3. Toxic reactions may be encountered.

4. The precise mode of action in lupus vulgaris is not known.

5. Calciferol therapy combined with injections of streptomycin is worthy of further trial.

## ABSTRACT OF DISCUSSION

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: Dr. Michelson has given an excellent evaluation of vitamin D therapy in cutaneous tuberculosis. I can substantiate, in their entirety, his observations.

Physicians in this country have now confirmed the effectiveness of calciferol in the treatment of lupus vulgaris, yet neither Charpy, Dowling and Thomas nor any of us know how or why calciferol works. Calciferol, which is produced by the irradiation of the ergosterol of yeast, is strongly antirachitic and relatively nontoxic in therapeutic doses. It was originally thought to be the provitamin D in the skin which was activated by irradiation. Waddell (The Provitamin D of Cholesterol, *J. Biol. Chem.* **105**:711, 1934) showed that irradiation of cholesterol produced a compound equal to cod liver oil in antirachitic potency, and, therefore, thirty times greater in that respect than irradiated ergosterol. The discrepancy in the antirachitic potency of irradiated ergosterol and cod liver oil was known before vitamin $D_3$, or 7-dehydrocholesterol, was known. The antirachitic activity of irradiated milk, cod liver oil and irradiated skin is due to this substance. What effect might it have in lupus vulgaris?

When ergosterol is irradiated, lumisterol, tachysterol, and then calciferol and suprasterol are produced. Tachysterol has little, if any, antirachitic property, but it does have a greater effect than calciferol in producing the excretion of phosphorus. Would it or the other closely related compounds be effective in lupus vulgaris?

Why do not those who have services where cutaneous tuberculosis is seen try the several other substances that make up the vitamin D family to determine their therapeutic effectiveness? Each member of the group has a somewhat different effect on metabolism; perhaps using them all might help us to learn how vitamin D acts in cutaneous tuberculosis.

It should again be emphasized that calciferol is a toxic drug. It produces hypercalcemia, hyperphosphatemia and a rise in the nonprotein nitrogen level of the blood. In large doses, it withdraws calcium and phosphorus from bones and increases their excretion in the urine. If given in large doses for long periods of time, osteitis fibrosa cystica, soft tissue calcification or even death, often from renal calcification and failure, may ensue.

Dr. Michelson has discussed the toxic symptoms. It behooves us all to follow our patients closely and make sure that the drug is withdrawn when toxic symptoms occur and that calciferol is not taken, even in moderately large doses, independently for long periods of time by our patients.

Dr. Marion Sulzberger, New York: Since beginning our studies of calciferol at the New York Skin and Cancer Unit, I have been amazed at the number of cases of lupus vulgaris we were able to find among the foreign born in New York. In studies carried out in our institute, Dr. Frances Pasher and her collaborators published data indicating that vehicles used for calciferol are apparently not so important as the European authors first seemed to think. Alcoholic and oily vehicles seemed to have roughly equivalent effects. I cannot agree entirely with Dr. Michelson regarding the explanation that the peculiar geographic distribution of lupus vulgaris is due simply to differences in nutrition and sunlight. Switzerland, in general, has a high nutritional standard, with plenty of eggs, butter and milk and with the hours of sunlight very high in many areas; yet lupus vulgaris is common there. In many parts of the United States, even in the slums and mining districts with few hours of sunlight and with poor nutrition, lupus vulgaris is almost entirely absent. In South America, there is very little, if any, lupus vulgaris, even when nutrition is poor and exposure to sunlight low. I think the explanation is much more complex than the one given by Dr. Michelson, although there is no denying that both sunlight and diet do play a role in the incidence of tuberculosis. I was deeply interested in hearing Dr. Michelson's excellent report, and particularly his complete confirmation of the Jadassohn-Lewandowsky law: Whenever and wherever pathogenic micro-organisms are being damaged or slowly destroyed by immune processes in the tissues, sarcoid structures tend to appear. I should like to confirm Dr. Michelson's statement that on rare occasions the lesions of lupus vulgaris may be observed to turn into sarcoid lesions and vice versa. Such cases were reported long before the use of calciferol. Moreover, concomitant with these transformations, the response of the skin to the tuberculin test changes from hyperergic to hypoergic, or vice versa. Has Dr. Michelson been able to carry out quantitative tuberculin tests of the skin in his cases of lupus vulgaris in which a transformation to sarcoid lesions was noted under therapy with calciferol to see whether then, also, the tuberculin sensitivity has shifted from hyperergy to hypoergy?

Dr. Paul O'Leary, Minneapolis: Our experience in the use of streptomycin in the treatment of cutaneous tuberculosis and tuberculids has not been sufficiently encouraging to continue to use the antibiotic drug alone; similarly, my limited experience with calciferol in the treatment of lupus vulgaris has been far from encouraging. However, the combination of calciferol and streptomycin seems to offer results superior to those obtained from the use of either of these agents alone. Studies of blood calcium and phosphorus levels are not always so revealing as is the patient's reaction to calciferol. Evidence of vitamin D intoxication may be manifested by loss of appetite, lassitude, gastrointestinal upsets, headache or nausea before evidence of hypercalcinemia appears in the form of increased blood levels.

It seems to me that lupus vulgaris should now be subjected to the newer cultural and inoculation experiments for tubercle bacilli. I recently reviewed some forty-four articles dealing with bacteriologic studies in lupus vulgaris; none of them included a report of the modern cultural and inoculation experiments that may now be carried out on animals.

Feldman, who has done outstanding work in experimental tuberculosis, believes that much is to be done to prove that the bacillus recognized in lupus vulgaris is the same organism which causes pulmonary tuberculosis. I believe that with

present knowledge one is limited to saying that lupus vulgaris is a disease seen in patients who have tuberculosis. The lack of improvement in lupus vulgaris and the apparent cure of pulmonary and other forms of tuberculosis after administration of streptomycin and, conversely, the improvement in lupus vulgaris and lack of benefit in pulmonary tuberculosis after administration of calciferol, raise questions that now need answering.

DR. PAUL E. BECHET, New York: About a week before I left the East, I saw, at the Montreal General Hospital during a meeting of the Atlantic Dermatological Conference, a group of 6 or 7 patients with chronic lupus vulgaris with extensive involvement. All sorts of treatment had been tried, with little success. Dr. Fred Burgess, who presented the patients, had been using calciferol in treatment, with spectacular results. One patient showed complete recession of the disease. All the others were greatly improved. The new treatment shows great promise and in my opinion is a step forward in the therapy of lupus vulgaris; however, it will take several years properly to determine its value.

DR. HARRY ARNOLD, Honolulu, T. H.: Dr. Sulzberger's remarks prompt me to mention an article (Lima, L. de S., and Souza Compos, N.: Immuno-Biologic Anomalies in Leprosy, *Internat. J. Leprosy* **16**:9, 1948.) in which inversion of the reaction to the Mitsuda-Rost test, both from positive to negative and from negative to positive, is described. Corresponding changes are usually observed in the clinical form of the disease.

DR. HENRY E. MICHELSON, Minneapolis: I believe that the most important thing to emphasize in Dr. Curtis's discussion is that results in treatment of lupus vulgaris come when one is using almost toxic doses of calciferol. Small doses are of no value. We have found it advisable in a few cases to reduce the dose to 10,000 units three times daily and have found this worth while. When one is considering lupus vulgaris, one must think of the soil and the type of infection. I definitely believe the condition to be due to tuberculosis, but it is an odd form of tuberculosis and it is dependent on a great many factors in the patient's nutritional make-up. In answer to Dr. Sulzberger, the cases in Switzerland are largely in patients from the peasant class. The disease is noted more often in certain valleys, where the hygiene is notably poor, than in others.

I have often stated that the pathologic factors of lupus vulgaris and those of sarcoid could not be distinguished from each other in certain cases; I am sure that this is true. I was surprised to find, after treatment with calciferol, that the histologic picture often became sarcoidal. I have not performed any tests to show that the tuberculin reaction changes with the histologic features, but I believe Macrae did. He stated that the tuberculin reactions increase in intensity and run parallel with elevation of the sedimentation rate. The phenomenon takes place during the first three weeks of treatment and then settles down.

Dr. O'Leary will have to read a tremendous amount of literature if he wishes to find all the reports on bacilli in lupus vulgaris. There are many, many of them. It must be remembered that lupus vulgaris was treated by surgeons long before it was by dermatologists. The disease was not considered tuberculous until after Koch's work. The reasons for considering it tuberculous now are many: The finding of the bacilli, the tuberculin reaction, the history and the frequent presence of other forms of tuberculosis are just a few of them.

# SOME DERMATOLOGIC EPONYMS

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AND
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EPONYMIC designation, like any abbreviation, is intended to be a short cut to description, but to serve this purpose even occasionally used terms should be widely understood. It is the purpose of this list to bring together for convenient reference most of the eponymic entities of interest to the dermatologist. Some entities which are not easily found in standard texts on dermatology, or which are rarely encountered, are listed with definitions and references. Other entities, either partially eponymic, of great familiarity, or whose synonyms are self explanatory, are simply listed for the sake of completeness. No biographic or historic data are included, as these aspects of the subject have been thoroughly covered by Goodman.[1]

ACHARD-THIERS SYNDROME. Obesity and hypertrichosis of the face of masculine distribution in women without other signs of virilism.[2]

ADDISON'S DISEASE.

ALBRIGHT'S SYNDROME. An endocrine disturbance consisting of polyostotic fibrous dysplasia, with cutaneous pigmentation in both sexes and precocious puberty in girls.[3]

ALMEIDA'S DISEASE. Paracoccidioidal granuloma; Brazilian blastomycosis.

ANDREWS' PUSTULAR BACTERID.

BAELZ'S DISEASE. Superficial suppurative cheilitis glandularis.

BALZER'S ADENOMA SEBACEUM.

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From the Department of Dermatology, University of Illinois College of Medicine, Service of Dr. Francis E. Senear (Dr. Haeberlin), and the Department of Dermatology, Northwestern University Medical School, Service of Dr. Edward A. Oliver (Dr. Garrard).

1. Goodman, H.: Eponyms of Dermatology, Arch. Dermat. & Syph. **9**:675 (June) 1924.

2. Shallow, T. A.: Adrenal Tumour Producing the Achard-Thiers Syndrome, Ann. Surg. **98**:297 (Aug.) 1933.

3. Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females, New England J. Med. **216**:727 (April 29) 1937.

BAZIN'S BUCCAL PSORIASIS. Leukoplakia buccalis.

BAZIN'S DISEASE. Tuberculosis indurativa; erythema induratum.

BEHCET'S SYNDROME. Triple symptom complex.

BEIGEL'S DISEASE. Trichorrhexis nodosa; chignon fungus.

BESNIER'S LUPUS PERNIO. Acrodermatitis pustulosa hiemalis (Crocker); necrotizing chilblains (Allen).

BESNIER'S PRURIGO. Atopic dermatitis; neurodermatitis disseminata; atopic eczema; flexural eczema.

BLOCH-SULZBERGER DISEASE. Incontinentia pigmenti.

BOCKHART'S IMPETIGO. Superficial staphylococcic folliculitis.

BORST-JADASSOHN INTRAEPIDERMAL EPITHELIOMA.

BOWEN'S DISEASE. Precancerous dermatosis.

BRILL'S DISEASE. Sporadic endemic typhus with erythematous macular and petechial exanthems.

BROOKE'S DISEASE. Keratosis follicularis contagiosa.

BRUSHFIELD-WYATT SYNDROME. Weber-Sturge syndrome.

BUERGER'S DISEASE. Thromboangiitis obliterans.

BÜRGER-GRÜTZ SYNDROME. Xanthoma disseminatum and hepatosplenomegaly with cutaneous and mucosal lipidosis.[4]

CARRION'S DISEASE. Verruga peruana; Oroya fever.

CAZENAVE'S DISEASE. Lupus erythematosus.

CIVATTE'S POIKILODERMA. Reticulated pigmented poikiloderma.

CLUTTON'S JOINTS. Syphilitic hydrarthrosis.

CSILLAG'S DISEASE. Dermatitis lichenoides chronica atrophicans; lichen sclerosis et atrophicus, lichen albus of Zumbush.

CUSHING'S DISEASE. Pituitary basophilism.

DARIER'S DISEASE. Keratosis follicularis; keratosis vegetans.

DARIER-FERRAND DISEASE. Dermatofibrosarcoma protuberans; progressive and recurrent dermatofibrosarcoma.

DARIER-ROUSSY SARCOID. Subcutaneous sarcoid.

DARLING'S DISEASE. Histoplasmosis.

DERCUM'S DISEASE. Adiposis dolorosa.

DEVERGIE'S DISEASE. Pityriasis rubra pilaris.

DUHRING'S DISEASE. Dermatitis herpetiformis.

DUKE'S DISEASE (EXANTHEMA SUBITUM). Fourth disease.

EHLERS-DANLOS SYNDROME. Hyperelasticity of the joints and skin, subcutaneous tumors and fragility of the skin with faulty healing leading to scar formation.[5]

ENGMAN'S INFECTIOUS ECZEMATOID DERMATITIS. Dermatitis infectiosa eczematoides.

ERB'S SYNDROME. Syphilitic spastic spinal paralysis (paraplegia due to syphilitic transverse myelitis).[6]

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4. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 649.

5. Ronchese, F.: Dermatorrhexis with Dermatochalasis and Arthrochalasis (So-Called Ehlers-Danlos Syndrome), Am. J. Dis. Child. **51**:1403 (June) 1936.

6. Peters, E. E.: The Spinal Fuid in Erb's Syphilitic Spinal Spastic Paraplegia, Am. J. Syph., Gonor. & Ven. Dis. (Jan.) 1941.

FELTY'S SYNDROME. Chronic deforming arthritis with splenomegaly, lymphadenopathy, leukopenia, cutaneous pigmentation and dusky nodules.[7]

FORDYCE'S DISEASE. Pseudocolloid of the lips.

FOX-FORDYCE DISEASE. Chronic itching papular eruption of the axilla and pubes.

FRANCIS' DISEASE. Tularemia.

FREY'S SYNDROME. Auriculotemporal nerve syndrome. Increased secretion of the parotid gland with homolateral hyperhidrosis in the distribution of the auriculotemporal nerve.[8]

GAUCHER'S DISEASE. Large cell splenomegaly, cerebroside histiocytosis.

GILCHRIST'S DISEASE. Brazilian blastomycosis.

GRÖNBLAD-STRANDBERG SYNDROME. Angioid streaks of the retina, associated with pseudoxanthoma elasticum.[9]

GOUGEROT AND BLUM DISEASE. Pigmented purpuric lichenoid dermatitis.

GULL'S DISEASE. Atrophy of thyroid gland with myxedema.

HABERMAN'S DISEASE. Pityriasis lichenoides et varioliformis acuta.

HAILEY AND HAILEY DISEASE. Chronic benign familial pemphigus; recurrent herpetiform dermatitis repens; bullous Darier's disease; dyskeratosis bullosa hereditaria.

HALLOPEAU'S ACRODERMATITIS. Acrodermatitis continua, dermatitis repens.

HALLOPEAU-LEREDDE ADENOMA SEBACEUM.

HAND-SCHÜLLER-CHRISTIAN DISEASE. Christian-Schüller disease; systemic reticuloendothelial granuloma.

HANSEN'S DISEASE. Leprosy; Leontiasis; spedalskhed; *Aussatz.*

HAXTHAUSEN'S DISEASE. Keratoderma climactericum.

HEBRA'S PITYRIASIS RUBRA.

HENOCH'S PURPURA. Purpura abdominalis.

HEERFORDT'S DISEASE. Uveoparotitis; Uveoparotid fever.

HODGKIN'S DISEASE. Malignant lymphogranulomatosis.

HOPF'S ACROKERATOSIS VERRUCIFORMIS. A hereditary condition characterized by verrucous lesions resembling those of epidermodysplasia verruciformis, occurring on the dorsa of the hands and feet with some involvement of the palms and flexor surfaces of the fingers, wrists and forearms but never occurring on the face. Histologically, the disease may be differentiated from epidermodysplasia verruciformis by the absence of basket-weave appearance of the stratum corneum.[10]

HUNT'S SYNDROME. Herpes zoster involving the geniculate ganglion, characterized by auricular and facial palsy, pain, vertigo and tinnitus with vesicles on the external ear.[11]

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7. Felty, A. R.: Chronic Arthritis in the Adult, Associated with Splenomegaly and Leucopenia: A Report of Five Cases of an Unusual Clinical Syndrome, Bull. Johns Hopkins Hosp. **35**:16 (Jan.) 1924.

8. Frey, L.: Le syndrome du nerf auriculo-temporal, Rev. neurol. **2**:97 (Aug.) 1923.

9. Grönblad, E.: Angioid Streaks—Pseudoxanthoma Elasticum, Acta ophth. **7**:329, 1929.

10. Loveman, A. B., and Graham, P. V.: Acrokeratosis Verruciformis (Hopf), Arch. Dermat. & Syph. **43**:971 (June) 1941.

11. Hill, F. T.: Herpes Zoster Oticus: Report of Three Cases, Ann. Otol., Rhin. & Laryng. **45**:666 (Sept.) 1936.

HUTCHINSON'S LUPUS PERNIO. Lupus erythematosis resembling chilblains.

HUTCHINSON'S MELANOTIC WHITLOW. Malignant melanoma arising under the nail.

HUTCHINSON'S SYNDROME. Hutchinson's triad (a combination of the following stigmas of congenital syphilis: interstitial keratitis, peg-shaped, notched incisors and nerve deafness[12]).

HYDE'S PRURIGO NODULARIS. Lichen obtusus corneus.

JACOBI'S POIKILODERMA VASCULARE ATROPHICANS.

JACOB'S ULCER. Rodent ulcer.

JACQUET'S ERYTHEMA. Napkin dermatitis.

JADASSOHN'S BLUE NEVUS.

JULIUSBERG'S DISEASE. Pityriasis lichenoides chronica, parapsoriasis en gouttes of Brocq (guttate parapsoriasis).

KAST'S SYNDROME. The association of hemangiomas with chondromas or dyschondroplasia.[13]

KAPOSI'S MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA.

KAPOSI'S VARICELLIFORM ERUPTION. Herpes simplex superimposed on chronic eczema.[14]

KREIBICH'S EXUDATIVE NEURODERMATITIS.

KYRLE'S DISEASE. Hyperkeratosis follicularis et parafollicularis in cutem penetrans.

LEINER'S DISEASE. Erythroderma desquamativa, universal dermatitis of children at the breast.

LETTERER-SIWE DISEASE. Lipidosis or granuloma of the reticuloendothelial system, with petechial exanthem and purpura but without cutaneous xanthoma.[15]

LEWANDOWSKY-LUTZ DISEASE. Epidermodysplasia verruciformis.

LEWANDOWSKY'S ROSACEA-LIKE TUBERCULID.

LIBMAN-SACKS SYNDROME. A variety of acute lupus erythematosus disseminatus.

LIPSCHÜTZ' DISEASE. Ulcus vulvae acutum.

LUBARSCH-PICK SYNDROME. Atypical amyloidosis with macroglossia.[16]

MAFFUCCI'S SYNDROME. Dyschondroplasia associated with hemangiomas.[17]

MAJOCCHI'S DISEASE. Purpura annularis telangiectodes.

MAJOCCHI'S GRANULOMA. A kerion type, superficial fungous infection.

MEIGE'S DISEASE. Milroy's disease.

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13. Carleton, A., and Robb-Smith, A. H. T.: Kast's Syndrome (Multiple Hemangiomata Associated with Chondromata or Ollier's Dyschondroplasia), Brit. J. Dermat. **51**:91 (Feb.) 1939.

14. Lynch, F. W., and Steves, R. J.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **55**:327 (March) 1947.

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16. Bernard, W. G.; Smith, F. B., and Woodhouse, J. L.: Atypical Amyloidosis with Macroglossia, J. Path. & Bact. **47**:311 (Sept.) 1938.

17. Carleton, A.; Elkington, J. St. C.; Greenfield, J. G., and Robb-Smith, A. H. T.: Maffucci's Syndrome (Dyschondroplasia with Haemangeiomata), Quart. J. Med. **11**:203 (Oct.) 1942.

MELENY'S ULCER. An acute, undermining and burrowing streptococcic infection of the skin and the subcutaneous tissues.[18]

MIBELLI'S ANGIOKERATOMA.

MIBELLI'S DISEASE. Porokeratosis.

MILIAN'S ERYTHEMA. Ninth day erythema.

MILROY'S DISEASE. Tropholymphedema; chronic hereditary trophedema; hereditary edema of the legs; Meige's disease; familial hereditary edema.

MOELLER'S GLOSSITIS. Chronic superficial excoriations of the tongue; chronic glossitis.

MORVAN'S DISEASE. Syringomyelia.

NEUMANN'S DISEASE. Pemphigus vegetans.

NICOLAS-FAVRE-DURAND DISEASE. Lymphogranuloma venereum.

NIEMANN-PICK DISEASE. Lipid histiocytosis.

OSLER-RENDU-WEBER SYNDROME. Hereditary hemorrhagic telangiectasia.

PAGET'S DISEASE. Eczema epitheliomatosum.

PARKS-WEBER SYNDROME. Hemangiectatic hypertrophy of the limb (hypertrophy of an entire extremity due to congenital ectasia of the blood vessels). Superficial hemangiomatous elements with verrucous lesions, pigmentations and ulceration may be present.[19]

PAUTRIER-WORINGER SYNDROME. Lipomelanotic reticulosis.

PLUMMER-VINSON SYNDROME. Dysphagia due to chronic glossitis, cheilitis and pharyngitis, with hypochromic anemia and koilonychia.[20]

PRINGLE'S ADENOMA SEBACEUM.

QUEYRAT'S ERYTHROPLASIA.

QUINCKE'S DISEASE. Angioneurotic edema.

QUINQUAD'S DISEASE. Folliculitis decalvans.

RAYNAUD'S DISEASE. Symmetric gangrene of the extremities.

REITER'S SYNDROME. Arthritis, urethritis and conjunctivitis, not due to the gonococcus, sometimes associated with keratosis blennorrhagia.[21]

ROMBERG'S DISEASE. Progressive hemiatrophy of the face. An atrophic process involving the skin, subcutaneous tissues and bone, in the distribution of the fifth cranial nerve. The disease usually occurs in the second decade of life.[22]

ROTHMUND'S SYNDROME.[23]

SAVILL'S DISEASE. Epidemic exfoliative dermatitis, a form of exfoliative dermatitis which occurred in epidemics among the older inhabitants of asylums and infirmaries in London, England.[24]

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22. Archambault, L., and Fromm, M. K.: Progressive Facial Hemiatrophy: Report of Three Cases, Arch. Neurol. & Psychiat. **27**:529 (March) 1932.

23. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed 7, Philadelphia. Lea & Febiger, 1948, p. 665.

24. Savill, T.: On an Epidemic Skin Disease, Brit. M. J. **2**:1197 (Dec. 6) 1891.

SCHAMBERG'S DISEASE. Progressive pigmentary dermatosis.

SCHAUMANN'S DISEASE. Lymphogranulomatosis benigna, a generalized form of sarcoidosis with lesions characteristically on the skin, in the bones and in various organs, including the lungs, liver, spleen and uveal tract.[25]

SCHÖNLEIN'S PURPURA. Purpura rheumatica; idiopathic nonthrombopenic purpura.

SCHWENINGER-BUZZI DISEASE. Multiple benign tumor-like lesions of the skin.

SENEAR-USHER SYNDROME. Pemphigus erythematodes.

SJÖGREN'S SYNDROME. An association of keratoconjunctivitis sicca, xerostomia, rhinitis sicca and laryngitis sicca, in which the skin may show dryness, blueness as in Raynaud's disease, telangiectasis of the lips and finger tips, scleroderma-like changes and alopecia.[26]

SPIEGLER-FENDT SARCOID. This entity is considered a lymphoblastoma. It occurs in a localized form, resembling Boeck's sarcoid, and in a disseminated form, with lesions clinically resembling the Darier-Roussy type.[27]

ST. ANTHONY'S FIRE. Erysipelas.

STEVENS-JOHNSON SYNDROME. A severe form of erythema multiforme, characterized by erosive lesions of the orificial mucous membranes, including those of the mouth, conjunctiva and genitalia, with fever, prostration and sometimes multiform lesions on the glabrous skin.[28]

STRYKER-HALBEISON SYNDROME. Erythroderma with macrocytic anemia.

STILL-CHAUFFARD DISEASE. Arthritis of the cervical portion of the spine, with anemia, leukopenia, splenomegaly, enlargement of the lymph nodes and cutaneous pigmentations, especially on the cheeks.[29]

SULZBERGER AND GARBE DISEASE. Exudative, discoid and lichenoid chronic dermatitis.

SUTTON'S DISEASE. Periadenitis mucosa necrotica recurrens; chronic aphthous stomatitis.

SWIFT'S DISEASE. Acrodynia; erythredema polyneuropathy.

SYMMER'S DISEASE. Brill-Symmer disease; giant follicular lymphoblastoma.

THIBIERGE-WEISSENBACH SYNDROME. The occurrence of calcinosis cutis circumscripta with scleroderma.[30]

UNNA-SANTI-POLLITZER DISEASE. Parakeratosis variegata.

VIDAL'S DISEASE. Lichen chronicus simplex; neurodermatitis.

VINCENT'S INFECTION. Trench mouth.

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29. Singer, H. A., and Levy, H. A.: Relationship of Felty's and Allied Syndromes to Sepsis Lenta, Arch. Int. Med. **57**:576 (March) 1936.

30. Brody, J., and Bellin, D. E.: Calcinosis with Scleroderma, Arch. Dermat. & Syph. **36**:85 (July) 1937.

VOGT-KOYANAGI SYNDROME. Bilateral uveitis, premature alopecia and graying of the hair and symmetric vitiligo, especially of the extremities, with dysacousia.[31]

VOLKMANN'S DISEASE. Apostematous cheilitis glandularis.

RECKLINGHAUSEN'S DISEASE. Neurofibromatosis.

WATERHOUSE-FRIDERICHSEN SYNDROME. Fulminating meningococcic septicemia, vascular collapse and widespread purpuric lesions of the skin.[32]

WEBER-CHRISTIAN SYNDROME. Relapsing febrile nodular nonsuppurative panniculitis.

WEBER-COCKAYNE SYNDROME. A form of epidermolysis bullosa, localized to the hands and feet.[33]

WEBER-STURGE SYNDROME. Brushfield-Wyatt Syndrome. Nevus flammeus, contralateral hemiparesis, epilepsy and calciferous shadows in the cerebral cortex on roentgenologic examination.[34]

WERNER'S SYNDROME. Scleroderma, poikiloderma, bilateral juvenile cataracts, pluriglandular dysfunction and precocious graying of the hair.[35]

WERLHOF'S PURPURA. Thrombopenic purpura.

WILSON-BROCQ DERMATITIS EXFOLIATIVA.

55 East Washington Street (3).

541 Lincoln Road.

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31. Carrasquillo, H. F.: Uveitis with Poliosis, Vitiligo, Alopecia and Dysacousia (Vogt-Koyanagi Syndrome), Arch. Ophth. **28**:385 (Sept.) 1942.

32. Wright, D. O., and Reppert, L. B.: Fulminating Meningococcemia with Vascular Collapse (Waterhouse-Friderichsen Syndrome): Report of Four Adult Patients Who Recovered, Arch. Int. Med. **77**:143 (Feb.) 1946.

33. Waisman, M.: Recurrent Bullous Eruption of the Feet and Hands, J. A. M. A. **124**:1247 (April 29) 1944.

34. Weber, F. P.: The Sturge-Kalischer Disease, and the Sturge-Weber Panathenaic Amphora at Toronto, Brit. M. J. **1**:708 (April 4) 1936.

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# RECENT OBSERVATIONS ON GRANULOMA INGUINALE, WITH REPORT ON STREPTOMYCIN THERAPY

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AND
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AUGUSTA, GA.

IN RECENT years decided advances have been made in various aspects of the study of granuloma inguinale, such as in diagnosis,[1] cultivation of the etiologic agent,[2] experimental reproduction of the disease [1a] and treatment.[3] One hundred patients [4] with laboratory-proved

Aided by a research grant from the United States Public Health Service.

From the University of Georgia School of Medicine.

1. (*a*) Greenblatt, R. B.; Dienst, R. B.; Pund, E. R., and Torpin, R.: Experimental and Clinical Granuloma Inguinale, J. A. M. A. **111**:1109-1115 (Sept. 16) 1939. (*b*) Anderson, K.; Goodpasture, E. W., and DeMonbreun, W. A.: Immunologic Relationship of Donovani Granulomatis to Granuloma Inguinale, J. Exper. Med. **81**:41-50 (Jan.) 1945. (*c*) Packer, H.; Turner, H. B., and Dulaney, A. D.: Granuloma Inguinale of the Vagina and Cervix Uteri with Bone Metastases, J. A. M. A. **136**:327-329 (Jan. 31) 1948. (*d*) Dienst, R. B.; Greenblatt, R. B., and Chen, C. H.: Laboratory Diagnosis of Granuloma Inguinale and Studies on the Cultivation of the Donovan Body, Am. J. Syph., Gonor. & Ven. Dis., to be published. (*e*) Chen, C. H.; Dienst, R. B., and Greenblatt, R. B.: Skin Reaction of Patients to Donovani Granulomatis Antigen, to be published.

2. Anderson, K.: The Cultivation from Granuloma of a Micro-Organism Having the Characteristics of Donovan Bodies in the Yolk Sac of Chick Embryos, Science **97**:560-561 (Jan. 18) 1943. Beveridge, W. I. B.: Action of Antimony and Some Other Bacteriostatic Substances on Donovania Granulomatis Isolated in Chick Embryo, J. Immunol. **53**:215-223 (July) 1946. Dienst, R. B.; Reinstein, C. R.; Kupperman, H. S., and Greenblatt, R. B.: Studies on the Causal Agent of Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **31**:614-617 (Nov.) 1947.

3. (*a*) Greenblatt, R. B.; Kupperman, H. S., and Dienst, R. B.: Streptomycin in the Therapy of Granuloma Inguinale, Proc. Soc. Exper. Biol. & Med. **64**:389-390 (April) 1947. (*b*) Greenblatt, R. B.; Dienst, R. B.; Kupperman, H. S., and Reinstein, C. R.: Granuloma Inguinale: Streptomycin Therapy and Research, J. Ven. Dis. Inform. **28**:183-188 (Sept.) 1947. (*c*) Kupperman, H. S.; Greenblatt, R. B., and Dienst, R. B.: Streptomycin in the Therapy of Granuloma Inguinale, J. A. M. A. **136**:84-89 (Jan. 10) 1948.

4. Since this article was submitted for publication 42 additional patients have been treated with streptomycin, and the patients comprising the total series of 142 cases have now been under observation for one to three years after treatment.

*(Footnote continued on next page)*

cases of granuloma inguinale who have been treated at the University of Georgia during the past twenty months formed the basis of this study.

The patients comprising this group were all Negroes. Their ages ranged from 18 to 70 years, and most of them were in the 20 to 40 year age groups. Sixty-five of them were men and 35, women (fig. 1). Though most of them had been previously treated with antimonial substances, one third of them had not had any form of treatment.

### LESIONS

As a rule patients gave a history of having had a nodule which had developed on the genitalia or elsewhere. This nodule had gradually softened, with the accumulation of purulent material. Later, the skin

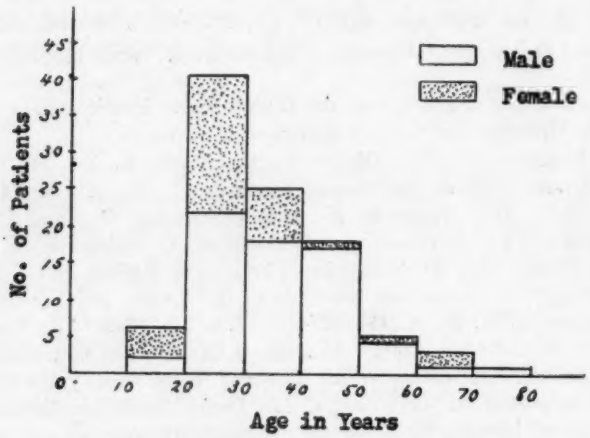


Fig. 1.—Distribution by sex in age groups.

surface had excoriated and an ulcerative process set in. In more chronic cases papillated vegetations and elephantiasis were commonly seen. While most patients presented the classic picture of a friable, "beefy red," ulcerogranulomatous lesion, about 15 per cent of the patients had lesions resembling a wide variety of either venereal (e. g., chancroid, lymphogranuloma venereum, syphilis) or nonvenereal (e. g., cancer, condyloma acuminatum) diseases. As a matter of fact, in a series of 95 referred patients who had been given a diagnosis or even treated as having had granuloma inguinale for months, only 66 (70 per cent) actually had

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In all, there has been a failure rate of about 10 per cent. Five of the patients for whom treatment failed proved recalcitrant to further streptomycin therapy. It is of interest to note that these 5 streptomycin-resistant patients were healed after the oral administration of aureomycin, the amounts varying from 25 to 70 Gm. in doses of 500 mg. every six hours.

the disease, the rest having the following disorders: squamous cell carcinoma, 6; chancroid, 6; lymphogranuloma venereum, 11; condyloma acuminatum, 3; pyogenic granuloma, 2, and syphilis, 1.

The most frequent sites of the lesions, in our series, were on the genital organs. These included the prepuce, the frenum, the glans penis, the shaft of the penis and the scrotum, in the male; the labium majus or minus, the clitoris, the fourchet, the vestibule, the vagina, the cervix and the uterus, in the female, and pubic and perineal regions, in both. Inguinal lesions ranked second. The adductor region of the thigh, which may be designated as the perigenital zone, and the perianal region were also commonly involved through direct extension and

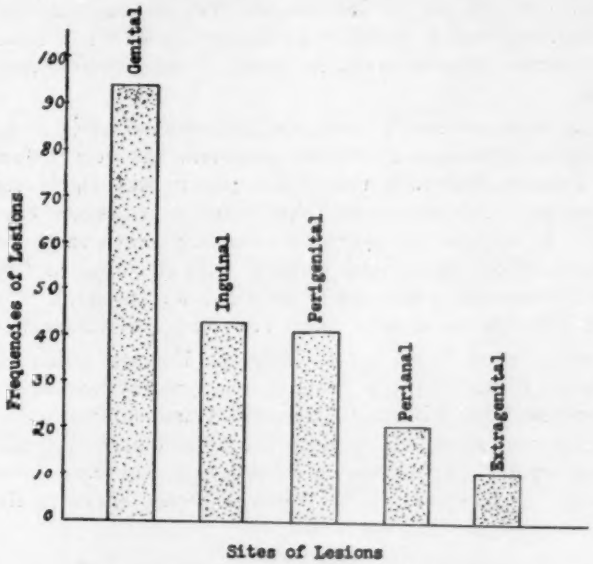


Fig. 2.—Distribution of sites of lesions.

contact with other lesions. Nevertheless, there were 2 patients with perianal lesions alone. Extragenital lesions, either concurrent or independent, were least common. They occurred in 7 per cent with involvement of almost any part of the body, such as the tongue, lip, gum, palate, postauricular region, neck, trunk, abdomen, buttock, finger and leg. The size of the lesion also varied a great deal, ranging from 1 to 300 sq. cm. in the lesions measured. Except in very chronic cases, it seemed to be proportional to the duration of the disease (fig. 2).

It was not infrequent to find other diseases associated with granuloma inguinale. Fusospirochetosis was by far the commonest. It occurred in 21 per cent of all cases. Other venereal diseases, such as chancroid, lymphogranuloma venereum, syphilis and gonorrhea, were

found to coexist. In 1 patient all major and minor venereal diseases were present, with the possible exception of chancroid. In addition, fusospirochetosis was superimposed on his granulomatous lesions.

## METHOD OF ESTABLISHING DIAGNOSIS

Direct tissue smear examination was routinely employed in our studies. Before the smear was taken, the most typical area, i. e., the most reddish-looking and friable area, was chosen and cleaned well with a cotton applicator. A small piece of the granulomatous tissue, about 2 cu. mm. and not larger, was nipped off with the corners of two slides and firmly pressed with a grinding motion between the slides until a thin smear was obtained. Then the slides were pulled apart by sliding sidewise one from the other. In this way two smears were made. After they had been allowed to dry they were stained with a modification of Wright's stain [4a] for one and one-half minutes; then an equal quantity of distilled water was added and staining continued for another three or four minutes. When unruptured inguinal pseudobuboes were found, smears were made from the aspirated pus.

With an oil immersion lens a search was made for the typical Donovan bodies in the cytoplasm of monocytes. If this procedure had been followed without finding the Donovan body and the clinical picture was highly suggestive of granuloma inguinale, repeated smears were taken on successive days for three or four days. Meanwhile, the superficial secondary contaminants, such as fusiform bacilli and spirochetes or other bacteria, were eliminated as far as possible with the use of penicillin or sulfonamide drugs, as was indicated. On more than one occasion, Donovan bodies were found after such preliminary treatment.

In rare cases (three in our series) in which Donovan bodies could not be found in original tissue smears, a specimen was removed for biopsy, and tissue smears and sections from this material revealed typical intramonocytic organisms. Biopsy of tissue also served to determine the possibility of other diseases, such as cancer and syphilis. No patient was included in this series unless diagnosis was established by demonstration of Donovan bodies, either in tissue smears or in biopsy specimens.

## TREATMENT

Since it was our purpose to determine the effectiveness of streptomycin, other medication which might effect the Donovan body, whether general or topical, was not used. Fusospirochetosis, if present, was first treated with one or two injections of 300,000 units of penicillin in oil and wax (U. S. P.) intramuscularly. Then streptomycin was given in six equally divided doses at four hour intervals by the intramuscular route. The first 32 patients received a daily dose of 0.3 to 2.0 Gm. for from six to sixty-two days, with an average of twenty-two days. Since the period of treatment was too prolonged and since there had been frequent recurrences, the dosage was later increased to 4 Gm. a day for five days, with a total dose of 20 Gm. For patients with very extensive lesions the dose was advisedly increased up to 40 Gm., but not more (table 1). In all instances the amount of streptomycin to be given at each injection was dissolved in 2 cc. of distilled water containing a small amount of procaine hydrochloride, the latter being used to alleviate local irritation and pain.

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4a. Formula: methanol (free from acetone), 485 cc.; glycerin, 15 cc., and Wright's stain (powder form), 1 Gm.

Streptomycin suppositories given at three hour intervals were tried on 4 patients. The first 2 patients, with both genital and inguinal lesions, were given rectal suppositories with a daily dose of 4 Gm. for nine days, plus 8 Gm. for seven days for one and 4 Gm. for ten days for the other. The next 2 patients, 1 with a lesion at the introitus vaginae and the other with a lesion on the lower abdomen wall, were each given 4 Gm. daily for five days per vagina. Dibucaine hydrochloride (nupercaine hydrochloride®) ointment was used in the patient with the vaginal lesion ten minutes before each insertion of the vaginal suppository, to prevent burning pain due to the suppository.

## TOXIC MANIFESTATIONS

Of all patients treated with streptomycin pruritus developed in 3 and burning sensations in the eye in 1. These conditions were readily controlled by the administration of diphenhydramine hydrochloride (benadryl hydrochloride®) or temporary suspension of streptomycin. However, a fifth patient had, in addition to pruritus, a generalized

TABLE 1.—*Dosage and Results*

| Total Number of Patients Treated, 100 (Male, 65; Female, 35) | | | | | |
|---|---|---|---|---|---|
| Dosage * | | | Results | | |
| 2 Gm. or Less per Day for Average of 22 Days | 4 Gm. per Day for 5 Days | 4 Gm. per Day for 6-10 Days | Successful | Recurrence | Failure |
| 32 | .. | .. | 24 (75%) | 6 (19%) | 2 (6%) |
| .. | 61 | .. | 57 (93%) | 4 (7%) | 0 (0%) |
| .. | .. | 7 | 7 (100%) | 0 (0%) | 0 (0%) |

* All doses were given intramuscularly.

urticarial and a circumoral vesicular eruption. He did not respond to the antihistaminic drug, and treatment with streptomycin had to be discontinued. Five months later he came back with a recurrent lesion and was retreated with the 4 Gm. per day schedule. This time only generalized urticaria appeared, and with diphenhydramine hydrochloride he was able to take a seven and one-half day (30 Gm.) treatment without further difficulty.

Transient mild pyrexia, unnoticed by patients themselves, starting on the second and subsiding on the third or fourth day, was observed in almost everyone treated with the 4 Gm. per day schedule. Involvement of the eighth nerve, on the other hand, was not encountered in our series.

## RESULTS

During the first period, when patients were receiving a daily dose of 2 Gm. or less, the response was good but rather slow. Donovan bodies often persisted up to ten days, and lesions took many weeks to

heal. Two patients failed to respond to 1 Gm. per day for twenty-eight days and 2 Gm. per day for thirty days, respectively (table 2). But with the 4 Gm. per day dosage, signs of improvement were usually noticed as early as twenty-four hours after the beginning of treatment. The feeling of soreness was distinctly alleviated; lesions became drier and cleaner, and healthy granulation tissue began to appear; smears taken at this time showed some degree of disintegration of Donovan bodies, with slight decrease in their number. After forty-eight hours, amelioration of symptoms was usually obtained, and Donovan bodies showed further disintegration and decrease in number. In favorable cases complete disappearance of Donovan bodies and beginning of epithelization were seen at the end of the third or fourth day and complete healing at the end of the fifth or sixth day. However, in

TABLE 2.—*Recurrences and Failures*

| Number of Patients, 12 (Male, 10; Female, 2) | | |
|---|---|---|
| Original Dosage | Dosage for Retreatment | Results |
| 0.3 Gm./day for 11 days ( 3.3 Gm.) | 4.0 Gm./day for 10 days (40.0 Gm.) | Healed |
| 0.3 Gm./day for 12 days ( 3.6 Gm.) | 4.0 Gm./day for 7½ days (30.0 Gm.) | Healed |
| 0.3 Gm./day for 35 days (10.5 Gm.) | 4.0 Gm./day for 5 days (20.0 Gm.) | Healed |
| 4.0 Gm./day for 5 days (20.0 Gm.) | 4.0 Gm./day for 10 days (40.0 Gm.) | Healed |
| 0.6 Gm./day for 11 days ( 6.6 Gm.) | 4.0 Gm./day for 7½ days (30.0 Gm.) | Healing |
| 1.0 Gm./day for 13 days (13.0 Gm.) | 4.0 Gm./day for 10 days (40.0 Gm.) | Healing |
| 4.0 Gm./day for 5 days (20.0 Gm.) | 4.0 Gm./day for 10 days (40.0 Gm.) | Healing |
| 1.0 Gm./day for 28 days (28.0 Gm.) | 1.5 Gm./day for 41 days (61.5 Gm.) | |
| | 4.0 Gm./day for 10 days (40.0 Gm.) | Failure |
| 2.0 Gm./day for 30 days (60.0 Gm.) | 4.0 Gm./day for 10 days (40.0 Gm.) | Failure |
| 1.0 Gm./day for 44 days (44.0 Gm.) | To be re-treated | |
| 4.0 Gm./day for 5 days (20.0 Gm.) | To be re-treated | |
| 4.0 Gm./day for 5 days (20.0 Gm.) | Patient died of recurrence (?) untreated | |

most cases Donovan bodies disappeared at the end of a five day course of streptomycin and complete healing, with scar formation, occurred in one to two weeks. In cases with more extensive lesions or in those in which the lesions remained moist or in apposition to other body surfaces, complete healing was sometimes delayed for from two to three months, in spite of the fact that Donovan bodies had disappeared within the usual time interval.

In those patients treated with rectal suppositories no improvement was felt or observed at all. The patient who received vaginal suppositories for her vaginal lesions, however, did have complete surface healing, with smears free from Donovan bodies after two weeks, an area of slight induration and discoloration being left. The second patient receiving vaginal suppositories for her abdominal lesion also had some improvement, with surface healing, but the area was still indurated and elevated. Smears taken at the end of treatment were

positive for Donovan bodies; however, at the end of six weeks healing was complete.

FOLLOW-UP STUDIES

All patients, after dismissal, were asked to return regularly for rechecks at least every two months and in special cases as often as every week. To date, about 80 per cent of our patients have been followed in this manner for from six to twenty months, over half of them having been followed for more than one year. During this period 10 patients have returned with a recurrent lesion, 6 from the group treated with 2 Gm. or less per day and 4 from the group treated with 4 Gm. per day for five days. There have been no recurrences in those treated with 4 Gm. per day for from six to ten days (table 1). It must be added that all recurrences up to now have occurred within four months after the completion of therapy.

Seven of the patients with recurrences have been re-treated with the 4 Gm. per day schedule for from five to ten days, with complete healing in each case. Two patients have not been re-treated. One patient, who failed to return, died several months later with what may be accepted as having been a recurrence. His relative said that he was "eaten away with sores all over his front and back."

The 2 patients who represented primary failures were re-treated with 4 Gm. per day for ten days, without success. They were then given antimonial substances. The first one received 3 cc. of anthiomaline® (antimony and lithium thiomalate), equivalent to 30 mg. of antimony, intramuscularly three times a week for one and one-half months, with the result that all lesions were healed before she was discharged from the hospital. Injections are being continued once a week for another six months to prevent a recurrence. The second received similar therapy for one month, but no response was obtained. Because stilbamidine® (4,4′-stilbenedicarboxamidine) proved so effective in treatment of leishmaniasis,[5] the last-mentioned patient was given a trial course of this drug, consisting of fifteen doses of 150 mg. each in 10 cc. of isotonic solution of sodium chloride, injected intravenously every other day. This treatment proved ineffective. Since the patient had a decidedly exuberant form of lesion, local applications of 25 per cent of resin of podophyllum N. F. in compound benzoin tincture U. S. P. were made three times a week for three weeks. The result was very good then, and all the excessive granulation tissue regressed. Injections of anthiomaline® were resumed, and roentgen therapy was given one week after treatment with resin of podophyllum was started. The dosage of roentgen radiation was 200 and 90 r on the first and

5. Adams, A. R. D., and Yroke, W.: Studies in Chemotherapy: XXXIII. A Case of Indian Kala-Azar Treated with 4:4′ Diamidine Stilbene, Ann. Trop. Med. **33**:323-326 (Dec.) 1939.

second days, respectively, and again 95 r per day for two days one month later. Within three months his lesions were completely healed, with scar formation. It must be added that, on account of the severe burning pain which usually follows the application of resin of podophyllum, its use is not indicated on very extensive lesions and lesions on more sensitive parts of the genitalia.

Both patients treated with rectal suppositories were immediately given a regular course of streptomycin, to which they responded readily. The patient treated with vaginal suppositories for her vaginal lesion had a recurrence one month later. A five day course of treatment cleared her lesion completely. All these 3 patients have been included in the group treated with 4 Gm. per day for five days. The lesion of the second patient treated with vaginal suppositories remains healed, and she is still under observation.

## COMMENT

Granuloma inguinale, according to our observations, may be most appropriately defined as a chronic infectious disease of doubtful transmission caused by the so-called Donovan bodies and characterized by a slowly growing granulomatous process, usually affecting the genital organs, the inguinal and perianal regions and occasionally other parts of the body. It occurs chiefly in warm climates and among Negroes. (In this series all were Negroes; however, we have encountered 3 white patients with granuloma inguinale.) However, cases have been reported from almost every part of the world, and no race is exempt.[6]

Contrary to the old general belief that granuloma inguinale primarily involved the inguinal region—hence the name—we found that genital lesions greatly outnumbered inguinal ones. In all our cases the number of lesions in the genital zone was 81, as compared with 36 in the inguinal region. (This is a fact that has been recognized by many investigators.[7]) Moreover, we have observed that in most cases with inguinal lesions there had been antecedent lesions on the genitalia. With regard to extragenital lesions, they may occur on any part of the body. Therefore, this disease is by no means limited to the inguinal region, nor is it most frequently found in that region.

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6. Harris, R.: Granuloma Venereum: General Discussion with Report of a Case of Laryngeal Involvement, Laryngoscope **40**:707-737 (Oct.) 1930.

7. Harris.[6] Fox, H.: Granuloma Inguinale: Its Occurrence in the United States, J. A. M. A. **87**:1785-1789 (Nov. 27) 1926. Lewis, S. J.: Granuloma Inguinale with Special Reference to Its Occurrence in the White Race, South. M. J. **25**:836-840 (Aug.) 1932. Cole, H. N.: Venereal Diseases with Particular Reference to Granuloma Inguinale and Lymphogranuloma Inguinale, Pennsylvania M. J. **109**: 580-585 (July) 1937. D'Aunoy, R., and von Haam, E.: Granuloma Inguinale. Am. J. Trop. Med. **17**:747-763 (Sept.) 1937.

The spread of lesions was usually by continuity and contiguity. However, lymphatic spread was necessarily common also, as there were many cases in which genital lesions were followed by or accompanied with inguinal lesions. In patients with both extragenital and genital lesions, the possibility of spread by a hematogenous route has been considered. Several attempts to culture Donovan bodies from the blood and bone marrow of such patients have been made but were unsuccessful. Recently Packer, Turner and Dulaney [1c] have demonstrated organisms having the morphologic features of Donovan bodies in the blood of a patient who had systemic infection, with metastases to bone.

Experimental inoculations by ordinary scratch method with granuloma tissue on several volunteers all met with failure. It was therefore decided to make repeated scratch inoculations on 1 patient. An area on the anterior aspect of his thigh was chosen and scratched to gentle bleeding every day. Immediately a piece of fresh granuloma tissue was rubbed onto that area each time and then kept in constant contact with the abraded skin by adhesive plaster. This procedure was continued for thirty-one consecutive days, and finally there was not the slightest sign of "take" observable grossly or microscopically. Hence it is very doubtful whether granuloma inguinale could develop on normal or simply abraded skin. Other factors must come into play also. Whether or not this is true with regard to mucous membranes is to be determined. Suggestions have been made that lesions of granuloma are usually superimposed on other lesions, like chancroid or lymphogranuloma venereum. Although we have not done any experiment along this line, we have been greatly impressed by the fact that a majority of our patients had positive reactions to either the Ducrey or the Frei test, or both, as we routinely tested them.

The diagnosis of granuloma inguinale by laboratory method is the simplest and most accurate of the venereal diseases. A positive diagnosis can usually be established within a few minutes. The entire procedure consists of making tissue smears from the lesion, staining these with Wright's stain and examining them under the oil immersion lens for the typical intramonocytic Donovan bodies. However, a proper technic is of paramount importance. A smear taken from a poorly selected area or a smear that is improperly prepared may often give rise to a false negative result. Experience has taught us that the procedures as briefly outlined previously are most convenient and satisfactory. Thorough cleaning of lesions before the taking of smears and the suppression of secondary contaminants by means of drugs are helpful in that the presence of necrotic debris and numerous bacteria hinders the finding of Donovan bodies. Too thick a tissue smear leads to a similar difficulty. The modification of the ordinary Wright staining method is

recommended for demonstration of the capsular material of the Donovan bodies. Donovan bodies with slightly overstained capsules are more readily seen by the examiner.

It must be stressed that in making an initial diagnosis one should depend only on observations of Donovan bodies in the cytoplasm of monocytes, because extracellular ones can be confused with other encapsulated organisms, especially the Friedländer bacillus. The presence of only extracellular Donovan bodies, however, is an indication for more prolonged searching or the making of more smears.

If one may judge from the data presented in preceding paragraphs that many cases of granuloma inguinale resembled those of other diseases, and vice versa, the importance of having a laboratory diagnosis in every case cannot be overemphasized. Laboratory diagnosis should be used as a final check in all clinically diagnosed or suspected cases of granuloma inguinale. It is only then that one can deal with this disease confidently and intelligently.

The treatment of granuloma inguinale has long been a problem taxing the ingenuity of the physician. Many unfortunate victims have succumbed to it eventually or have died of intercurrent diseases. The socioeconomic consequences of this problem were presented by one of us.[8] But since the demonstration of the specificity of antimonial compounds against this disease in 1912,[9] the situation has become more favorable. Success in treatment was reported from different parts of the world. However, in our institution, as everywhere, more and more recurrences were seen as time went on, even in patients who had been treated for a long period. Later, some of these acquired chemoresistance and once again became a public burden. In view of the protracted course of treatment required with antimonial substances and the frequency of recurrence,[10] one could not deny that this problem was far from being solved satisfactorily. Search for a better form of remedy went on. Every new therapeutic agent, such as the sulfonamide drugs,[10] tyrothricin [11] and penicillin,[12] which was found to have an effect on

8. Greenblatt, R. B.: Socioeconomic Aspects of Granuloma Inguinale, J. Ven. Dis. Inform. **28**:181-183 (Sept.) 1947.

9. Aragao, H. D., and Vianna, G.: Mem. Inst. Oswald Cruz **4**:211 (Jan.) 1912.

10. Allison, G. G.: Granuloma Inguinale: A Study of Two Hundred Cases, J. M. A. Georgia **35**:103-107 (April) 1946.

11. Greenblatt, R. B.; Kupperman, H. S.; Dienst, R. B., and Chen, C. H.: Unpublished data.

12. Turner, F. B.: Granuloma Inguinale: Treatment of Seven Cases with Penicillin, M. J. Australia **2**:366-367 (Dec. 1) 1945. Haserick, J. R.: A Failure of Penicillin in the Treatment of Granuloma Inguinale, Arch. Dermat. & Syph. **52**:182 (Sept.) 1945. Nelson, R. A.: Penicillin in the Treatment of Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **28**:611-619 (Sept.) 1944.

pathogenic micro-organisms was put on trial. Unfortunately, none of them showed any promise toward the eradication of this dreaded malady and the salvation of these poor sufferers.

Then hope for a better remedy for granuloma inguinale revived when streptomycin was found to be very effective against a number of gram-negative bacteria and fungi which would not yield to any ordinary therapeutic agents. In 1946 we started to treat patients with granuloma inguinale with streptomycin.[3a] The striking results, as seen clinically and microscopically,[3] unequivocally put this substance first in the long list of drugs and methods of treatment for granuloma inguinale.

The treatment of granuloma inguinale with streptomycin required considerable variations in order for an optimal dosage to be established. Accumulated experience has taught us that a daily dose of 2 Gm. or less for even as long as an average of twenty-two days was not ideal. We had 6 recurrences and 2 ultimate failures among 32 patients thus treated. But with the daily dose increased to 4 Gm. the results were manifold, in spite of the fact that the period of treatment was cut down to less than one-fourth. Therefore, a sufficient daily dose is probably of primary importance. Since we have had in mind establishing a uniform dosage schedule we have been treating patients with 4 Gm. a day for five days for all early and average cases and for from six to ten days for very extensive cases, regardless of whether or not smear examinations were negative for the Donovan bodies at the end of the course. If the patient had not had any improvement with the ten day course, he or she was watched for several weeks to months before being considered resistant to streptomycin. With this regimen we have observed that all those whose smears still showed Donovan bodies at the end of a five day course eventually had complete healing without additional therapy. A specimen taken for biopsy from the healed scar of 1 of these patients was found to be free from Donovan bodies. So far, for a period of eight months, the lesion remains healed. Since all recurrences in this series have taken place within the first four months this patient stands a very good chance of becoming permanently cured. Nevertheless, this result should not lead us to think that this dosage schedule is as yet standard, because there have been 4 patients in whom recurrence was noted in the group treated with the five day course. The fact that all patients treated with the six to ten day course have not had any recurrence probably means that the course of treatment should be increased to ten days, at least in cases in which smears are positive at the end of the five day course and in cases with extensive lesions. We feel that by giving sufficient daily and total doses it is possible for one to reduce recurrence to a minimum.

The effect of streptomycin when used in the form of a suppository is apparently greatly decreased. Rectal suppositories, even when given in a dosage as high as 8 Gm. per day, were ineffective. Vaginal suppositories seemed to have some effect both locally, as illustrated in the case with the vaginal lesion, and generally, as illustrated in the case with abdominal lesions. But, in view of the rapidity of recurrence in the former and the sluggishness of healing in the latter, in which there was only a very small lesion, use of suppositories should be limited to experimental work.

The treatment of fusospirochetosis before starting treatment of the granuloma with streptomycin, though not essential, is helpful. It enhances the speed of healing of the lesion under subsequent streptomycin therapy by decreasing the exudate which keeps the lesion moist. Dryness is an important environmental factor in the process of healing.

Since both patients who failed to respond and developed resistance to streptomycin thereafter were treated originally with a relatively small dose, it may well be that a small dose is a factor contributing to the development of resistance. Therefore, it is probably essential for one to begin treatment with streptomycin, as with other chemotherapeutic drugs and antibiotics, with a dose large enough to avoid creating resistance. Knop in his experimental study made a similar statement.[13]

The mechanism of the febrile reaction developed soon after the institution of streptomycin therapy is not understood. It has been suggested that it might be a type of the Jarisch-Herxheimer reaction,[14] similar to that encountered in the treatment of syphilis with arsphenamine and penicillin, due to the disintegration of Donovan bodies. There is little reason to account for the absence of involvement of the eighth nerve, except that all our patients were treated with a comparatively short course, the longest of which was sixty-two days, with a daily dose of less than 1 Gm.

Finally, the case of the chemoresistant and streptomycin-resistant patient treated with resin of podophyllum, roentgen radiation and anthiomaline® deserves consideration. We do not think anthiomaline® was responsible for the improvement, for the following reasons: (1) Anthiomaline® had been used for months without any significant effect before treatment with streptomycin was begun; (2) as a rule, antimonial therapy does not cause such a rapid remission, and (3) the stages of improvement did not coincide with the administration of anthiomaline® but ran parallel with the application of resin of podo-

13. Knop, C. Q.: Experimental Study of the Development of Resistance to Streptomycin by Some Bacteria Commonly Found in Urinary Infection, Proc. Staff Meet., Mayo Clin. **21**:273-276 (July 24) 1946.

14. Moore, J. E.: Personal communication to R. B. Greenblatt.

phyllum. While both resin of podophyllum [15] and roentgen radiation [16] have been used successfully in treatment of granuloma inguinale, it is hard to say which of these should be given the credit. Judging from the clinical response, resin of podophyllum was probably the chief factor in this case. The action of resin of podophyllum on granuloma tissue has been thought to be one of dehydration.[15] However, we think its escharotic action was responsible for the results. Whether or not it has some specific action on Donovan bodies is a problem requiring further studies.

## SUMMARY AND CONCLUSIONS

The treatment of 100 laboratory-proved cases of granuloma inguinale with streptomycin is presented in detail, and the proper technic for taking and preparing tissue smears for examination is described.

In view of the frequency of improper diagnoses, a laboratory confirmation should be required in every case, and an initial diagnosis should be based on the finding of intramonocytic Donovan bodies.

Streptomycin is by far the most effective, if not the ideal, agent in the treatment of granuloma inguinale. A specimen taken for biopsy from the healed scar of 1 patient shortly after treatment failed to reveal any Donovan bodies.

The optimal dosage for streptomycin is 4 Gm. per day, given intramuscularly in divided doses, for from five to ten days. The ten day course is probably to be preferred, at least in those cases in which Donovan bodies are still present at the end of a five day course and in cases with very extensive lesions. With this regimen, toxic manifestations are rare.

It is emphasized that streptomycin should be given in sufficient primary doses in order for resistance to this antibiotic to be avoided. A preliminary treatment of secondary infections enhances the healing of lesions under subsequent streptomycin therapy.

Stilbamidine® (4, 4′-stilbenedicarboxamidine) apparently is ineffective in the treatment of granuloma inguinale, whereas resin of podophyllum N. F. is a useful aid. Further use of resin of podophyllum is warranted.

Experiments conducted along the line of transmission show that granuloma inguinale probably does not develop on normal or simply abraded skin.

University of Georgia School of Medicine.

15. Tomskey, G. C.; Vickery, G. W., and Getzoff, P. L.: Successful Treatment of Granuloma Inguinale with Special Reference to the Use of Podophyllin, J. Urol. **48**:401-406 (Oct.) 1942.

16. Deibert, A. V.; Greenblatt, R. B.; Pund, E. R., and Cannefax, G.: X-Ray Therapy of Granuloma Inguinale, to be published.

# ERYTHEMA ELEVATUM DIUTINUM

## Report of Three Cases

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ST. LOUIS

THE NAME erythema elevatum diutinum was used by Crocker and Williams [1] in 1894 to describe a cutaneous eruption in a 6 year old girl. The patient did not have "rheumatism." A microscopic examination of a piece of excised skin showed a fibrocellular structure in the corium but no changes in the blood vessels except a slight cellular infiltration in the outer coats. In 1929 Weidman and Besancon [2] reported 2 cases of a condition which they described as erythema elevatum diutinum. The name used by Crocker and Williams was retained for the disease, although Weidman and Besancon described histopathologic changes which to them were pathognomonic and did not correspond with those previously described under that name by any other investigator.

Three additional cases presenting this type of histopathologic change have been reported since then: 1 by Combes and Bluefarb in 1940,[3] another by Engman, Pfaff and Cooper in 1942 [4] and the third by Ketron in 1944.[5] Ketron suggested that the number of cases was

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Studies, observations and reports from the Departments of Dermatology of the Washington University School of Medicine and of the Barnard Free Skin and Cancer Hospital.

1. Crocker, H. R., and Williams, C.: Erythema Elevatum Diutinum, Brit. J. Dermat. **6**:1-9 and 33-38, 1894.

2. Weidman, F. D., and Besancon, J. H.: Erythema Elevatum Diutinum: Rôle of Streptococci, and Relationship to Other Rheumatic Dermatoses, Arch. Dermat. & Syph. **20**:593-620 (Nov.) 1929.

3. Combes, F. C., and Bluefarb, S. M.: Erythema Elevatum Diutinum: Report of a Case, Arch. Dermat. & Syph. **42**:441-446 (Sept.) 1940.

4. Engman, M. F., Jr.; Pfaff, R. O., and Cooper, Z. K.: Erythema Elevatum Diutinum: Report of Case with Histologic and Bacteriologic Studies, Arch. Dermat. & Syph. **45**:334-341 (Feb.) 1942.

5. Ketron, L. W.: Erythema Elevatum Diutinum, Arch. Dermat. & Syph. **50**:363-372 (Dec.) 1944.

large enough to establish a new entity, emphasizing the microscopic criteria set forth by Weidman and Besancon. He suggested that the name erythema elevatum diutinum be retained temporarily, although the microscopic observations in the 5 cases were not compatible with those described by Crocker and Williams under that title.

We report 3 cases in which the diagnosis of erythema elevatum diutinum was made because of the characteristic microscopic picture seen at biopsy. These changes were essentially the same as those described by Weidman and Besancon. Two of the patients responded to treatment; when last observed they had no cutaneous lesions. The third patient has received no therapy as yet.

## REPORT OF CASES

CASE 1.—R. B., a 56 year old white fireman, was admitted to the Barnes Hospital on March 8, 1945. The chief complaint was a cutaneous eruption of eight years' duration. This eruption had begun on the feet and then appeared on the elbows, hands, knees and buttocks. In these eight years the eruption had never disappeared, but at times it would fade somewhat, only to reappear. The lesions had never been painful or pruritic, but there had been a "ticking" feeling in them (apparently pulsation). There were no other complaints. The patient had consulted a physician for this eruption in 1935, and a piece of skin had been removed from a lesion of the knee.

The family history disclosed that his mother had had "rheumatic arthritis" for eighteen years and that his father had died of "heart trouble." The patient had had a cough productive of thick, yellow sputum for the three months before admission. There were no neuromuscular complaints.

The examination of the skin disclosed flat nodules and plaques, which were dull red, over the elbows, the dorsal and palmar surfaces of the fingers, the knees, the buttocks, the feet and the ankles. A few of the nodules were arranged in circles or segments of circles. Over the elbows and feet the nodules tended to be discrete. There was some evidence of involuted lesions in that there were brown stains near areas of well developed lesions.

The general physical condition was entirely within normal limits. The red blood cell count was 5,180,000, with 15.2 Gm. (98 per cent) of hemoglobin. The white blood cell count was 8,250 cells, with 65 polymorphonuclear leukocytes (33 of which were stab forms), 24 lymphocytes and 11 monocytes. Urinalysis showed nothing abnormal, and the Kahn test for syphilis gave a negative reaction.

The patient's course in the hospital was uneventful. A piece of skin was removed on March 9, 1945, and the patient was discharged on March 10.

The patient was subsequently treated with triweekly injections of 5 per cent casein and 2.5 per cent sodium iodohydroxyquinolinesulfonate (activin®). These injections were continued for six months, the dose being 1 cc., given intramuscularly. The lesions on the buttocks were somewhat recalcitrant and were given a series of roentgen ray treatments, with subsequent complete disappearance of the lesions. Each treatment consisted of 88 r, with 85 kilovolts, 4 milliamperes and an 0.8 mm. aluminum half-value layer, with no filter and at a distance of 10 inches (25.4 cm.). The treatment with 5 per cent casein and 2.5 per cent sodium iodohydroxyquinolinesulfonate was resumed, resulting in the complete disappearance of the lesions by June 1946. The frequency of administration of the drug, which

had been given three times a week and then twice a week, was reduced to once a week; and when the patient was last observed, in November 1946, all the lesions remained completely involuted, and there was an apparent cure.

*Histologic Examination.*—In a specimen taken for biopsy from a lesion on the knee in November 1935, a small papule about 3 to 4 mm. in diameter was included. The epidermis showed relatively little change except for moderate hyperkeratosis and a few small areas of parakeratosis. On the surface of the epidermis in one small area there was a superficial crust made up of fibrin in which leukocytes

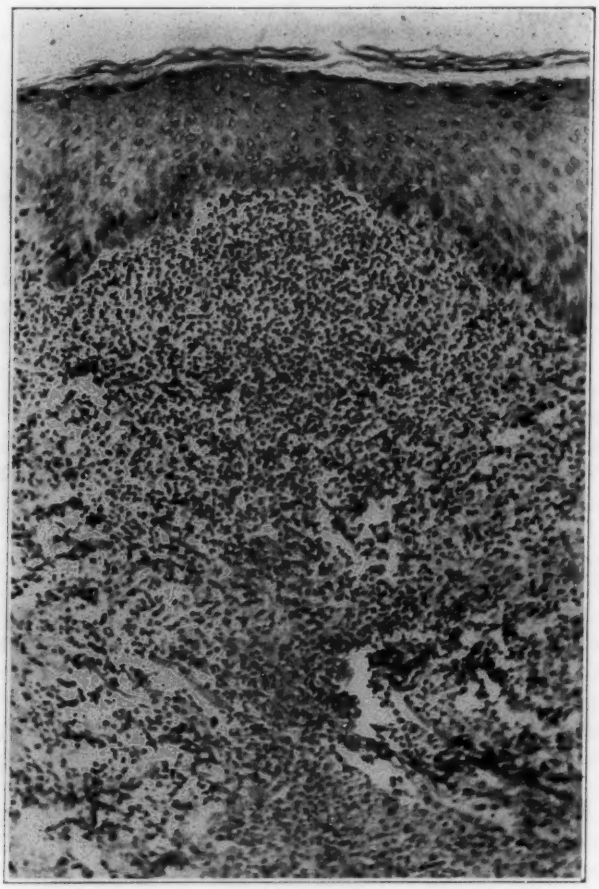

Fig. 1 (case 1).—Photomicrograph of the specimen taken in November 1935, showing an early lesion with a very dense cellular infiltrate, made up principally of polymorphonuclear leukocytes, in the dermis.

were embedded, but there was no ulceration beneath it. Although there was moderate acanthosis, the rete pegs were short and stubby. The epidermis as a whole showed intracellular and intercellular edema.

Throughout the upper half of the dermis there was a dense cellular infiltrate made up of large numbers of polymorphonuclear leukocytes together with a few lymphocytes and epithelioid cells (fig. 1). There were several foci in the dermis in which the cells of the infiltrate showed karyorrhexis, but there was no

necrosis. The blood vessels were dilated, and their walls were thickened. The endothelial cells lining them were hyperplastic, and their nuclei appeared swollen. About the vessels was a mantle of eosinophilic, hyalinized, fibrous material which resembled the "toxic hyalin" described by Weidman and Besancon. The dermis showed moderate edema.

In the specimen removed from the elbow region in March 1945 the changes corresponded to those observed late in the course of the disease by Ketron[5] and described in his report on biopsy 4 in his case. The cellular infiltrate, which

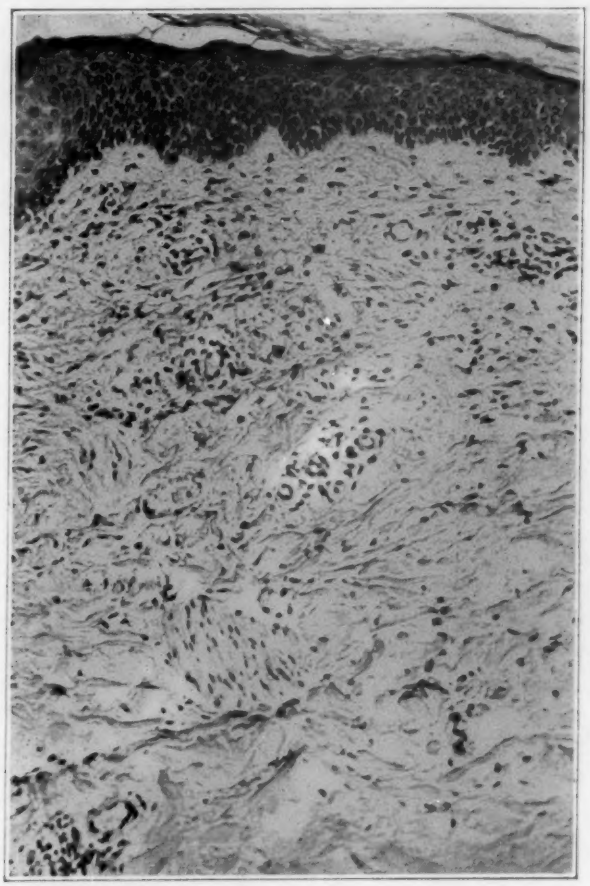

Fig. 2 (case 1).—Photomicrograph of the specimen taken in March 1945, showing a relatively late lesion, in which there is a reduction in the amount of cellular infiltrate in the dermis and some fibrosis.

tended to be perivascular, was reduced in amount and was made up of polymorphonuclear leukocytes, lymphocytes and epithelioid cells (fig. 2). Scattered between the collagen bundles were small basophilic granules, which probably represented fragmented nuclei, some of which had been engulfed by phagocytes. The blood vessels in this specimen, also, were surrounded by a distinct mantle of hyalinized, fibrous material (fig. 3). The dermis was moderately edematous, but early fibrotic changes were present.

The changes in the epidermis were minimal and consisted of moderate hyperkeratosis and slight acanthosis, although the rete pegs were shortened and in places almost obliterated. There was some intracellular edema.

CASE 2.—N. J., a 59 year old white coal miner, was admitted to the Barnes Hospital on Sept. 27, 1942. The chief complaint was an eruption of the skin of several years' duration and weakness of about three weeks' duration. About two and one-half years before admission the patient had noticed a profuse itching eruption on the hands, forearms and abdomen. Six months before the present

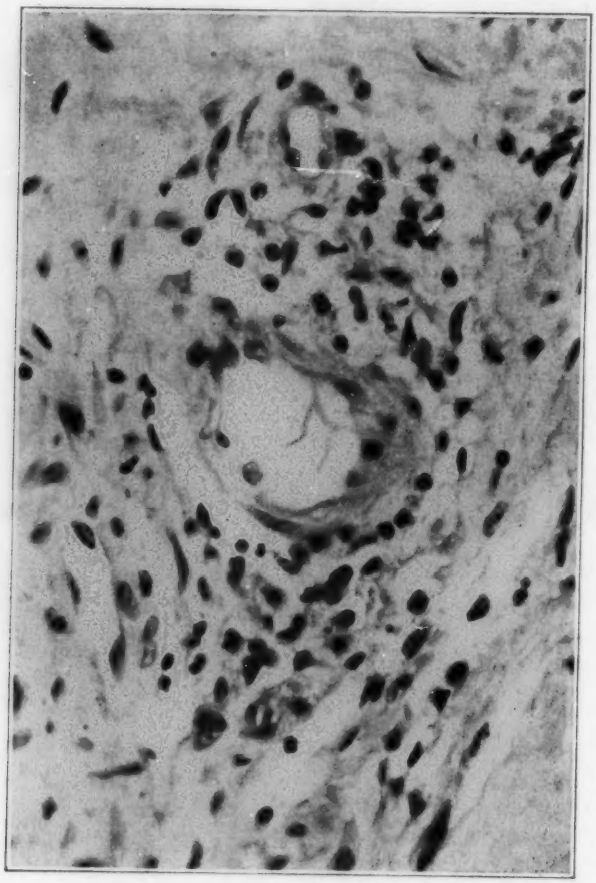

Fig. 3 (case 1).—High power photomicrograph of a small blood vessel in the specimen taken in March 1945. Note the deposit of "toxic hyalin" in the vessel wall and the infiltrate of polymorphonuclear leukocytes and lymphocytes surrounding it.

admission, in a hospital in Illinois, he had been treated for the cutaneous eruption with injections of nitromersol and with sulfathiazole and sulfanilamide, administered orally. The eruption had improved somewhat, but many of the patches persisted.

There was a past history of a slight cough, especially in the winter time, and of occasional fever, related only to a "cold." The patient had never had pains in the joints.

On the dorsal surfaces of the hands, the extensor surfaces of the wrists, the elbows and the area near the suprasternal notch there were dull red to bluish red circular and oval plaques, 2 to 6 cm. in diameter. There were a few circinate lesions over the scapulas. Several of the plaques were described as "spongy" to touch, but there was no definite infiltration. The lesions on the backs of the hands were exfoliating slightly. This condition was thought to be due to local applications.

General physical examination revealed a well developed and well nourished white man in no obvious discomfort. All the findings were within normal limits except that the cervical and inguinal lymph nodes were small and firm but not tender. There were pyorrhea and some decay of the teeth. The pharynx was reddened.

The red blood cell count was 4,940,000, with 93 per cent hemoglobin. The white blood cell count was 14,500, and the differential cell count revealed 72 polymorphonuclear leukocytes, 20 lymphocytes and 8 monocytes per hundred cells. The fasting blood sugar was 69 mg., the nonprotein nitrogen 21 mg. and the uric acid 3.2 mg., per hundred cubic centimeters. The Kahn test gave a negative reaction. One blood culture was reported as showing no growth. Agglutination reactions for Eberthella typhosa, paratyphoid organisms, organisms of the Brucella group and Proteus vulgaris $X_{19}$ were negative. The interpretation of the electrocardiogram was indeterminate. The diagnosis based on the roentgenographic examination of the chest was arrested pulmonary tuberculosis of the upper lobe of the right lung and peribronchial fibrosis of indeterminate nature.

The patient's course in the hospital was uneventful except that there was a slight elevation of temperature in the afternoon. The highest temperature recorded was 100 F. (37.8 C.).

On October 7, 50,000,000 killed typhoid bacilli were injected into a vein. The temperature (rectal) rose to 103.3 F. (39.6 C.). On October 11, 75,000,000 killed typhoid bacilli were injected into the vein, with a rise in temperature to 100.2 F. (38 C.). The lesions had improved on October 12. On October 14, 125,000,000 killed typhoid bacilli were injected intravenously, with a subsequent rise in temperature to 102 F. (38.8 C.). The patient was discharged on October 18. At that time there was involution of all the cutaneous lesions, leaving only slight erythematous and pigmented areas to mark their former sites.

The patient appeared again for observation on November 21, with a few plaques on the backs of both hands. They were treated with roentgen rays at weekly intervals for six weeks. Each treatment consisted of 88 r, with 85 kilovolts, 4 milliamperes and an 0.8 mm. aluminum, half-value layer, with no filter and at a distance of 10 inches (25.4 cm.). When the patient was examined on March 13, 1943, no lesions could be found. He was seen at monthly intervals up to Nov. 27, 1943, and no recurrence was observed.

*Histologic Examination.*—In a biopsy specimen removed in September 1942 from the right supraclavicular area the most striking changes were observed in the dermis. The blood vessels were dilated and the endothelial cells lining them were hyperplastic, but the lumens were not obliterated. About some of the vessels were small deposits of "toxic hyalin," but this change was not as conspicuous in this case as it was in case 1. In the subpapillary portion of the dermis there was a cellular infiltrate made up principally of polymorphonuclear leukocytes, together with some lymphocytes and epithelioid cells (figs. 4 and 5). Scattered among the cells of the infiltrate was extracellular basophilic granular material, which probably represented fragments of nuclei. The dermis was moderately edematous.

The epidermis showed hyperkeratosis and some acanthosis. The rete pegs, although relatively regular, were short and stubby.

CASE 3.—S. T., a 5 year old white girl, was admitted to the dermatologic clinic of the Barnard Free Skin and Cancer Hospital on Feb. 18, 1944. Her mother had noticed "spots" on the arms, left buttock and left leg for eight months. An individual "spot" might fade gradually over a period of several weeks, only to reappear in about the same area. The patient stated that the eruption did not itch, although her mother observed that she had scratched a few papules.

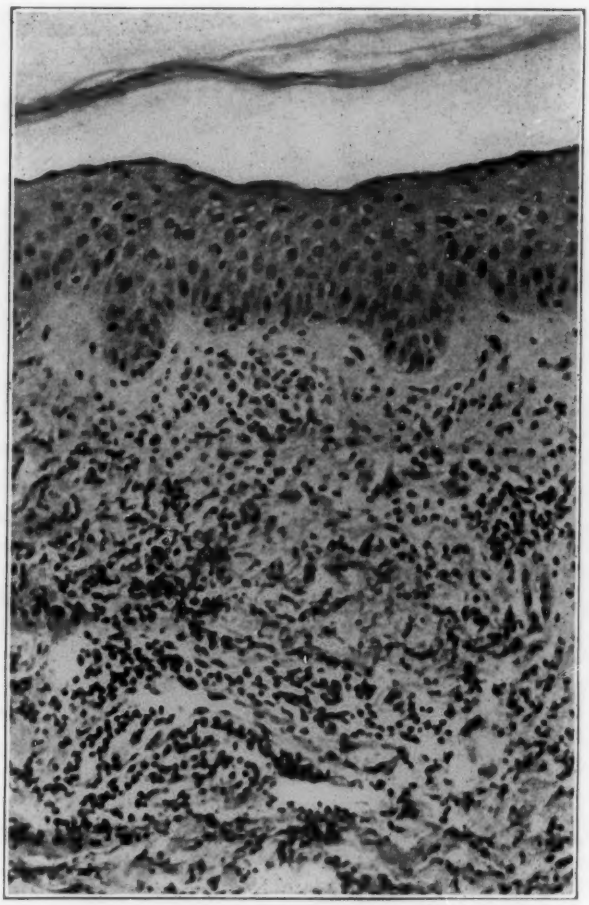

Fig. 4 (case 2).—Photomicrograph of an early lesion, showing a dense cellular infiltrate, in which polymorphonuclear leukocytes predominate, in the dermis.

There was a history of whooping cough at the age of 1 year and measles at the age of 3 years. The patient had been vaccinated and given injections of diphtheria toxoid U.S.P. at the age of 1. Her mother and father had been married for twelve years and were both in good health; there were 2 other siblings, aged 10 and 11, and the mother had had no miscarriages. One of the mother's sisters, who had died of tuberculosis, had seen the patient briefly when the patient was 2 years old. The child had no history of pain in the joints or muscular aches.

Examination of the skin revealed a sparse eruption of small (2 to 3 mm. in diameter), yellowish brown papules on the trunk, the left arm, the legs and the lower part of the left buttock. There were small inflammatory zones about a few of the papules and a fine grayish white scale over some of them.

The general physical condition was entirely within normal limits. There was no enlargement of the lymph nodes, and the tonsils were very small.

A piece of skin was removed from a lesion of the right buttock on February 18. The patient was treated with local antipruritics, without improvement.

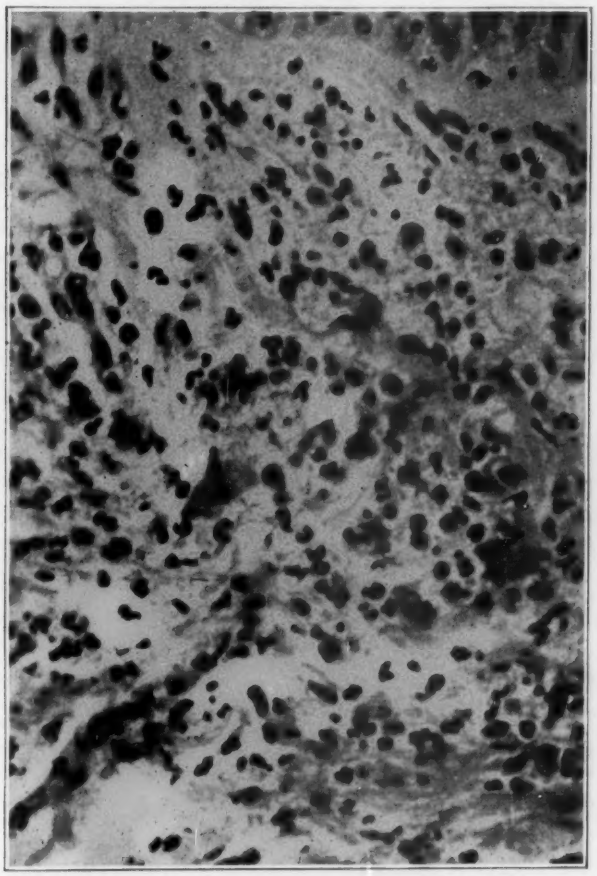

Fig. 5 (case 2).—High power photomicrograph of a portion of the dermis, showing the character of the cellular infiltrate. Polymorphonuclear leukocytes predominate.

On Nov. 17, 1946 the patient returned to the clinic because the eruption had persisted. The patient's mother stated that there had been some improvement in the cutaneous eruption, especially during the summer months, but that it had never completely disappeared. The patient had been in very good health for the past two years, although she had complained occasionally of "leg aches," which, however, had not prevented her playing out of doors.

An examination of the skin revealed two small (2 to 3 mm. in diameter), smooth, yellow-brown papules over the left buttock. There was a faint pinkish stain about the old scar at the site of removal of tissue for biopsy, but there were no papular lesions in that area. On the anterior surfaces of the right thigh there was one large, red papule (5 mm. in diameter), with a faint pink halo about it. There was a fine, pale yellow scale over the surface of this papule. About this papule were three smaller, brownish yellow ones (2 to 3 mm. in diameter).

The general physical condition was again entirely within normal limits. The red blood cell count was 4,560,000, with 11.5 Gm. of hemoglobin. The white blood cell count was 8,900, with 54 per cent polymorphonuclear leukocytes, 6 per cent eosinophilic leukocytes, 32 per cent lymphocytes and 8 per cent monocytes. The examination of the urine revealed a specific gravity of 1.025, an acid reaction and no albumin or sugar. On microscopic examination there was normal sediment.

*Histologic Examination.*—In a biopsy specimen taken in February 1944, the epidermis showed slight hyperkeratosis and moderate acanthosis. The rete pegs were regular in contour but were not greatly lengthened. The epidermis showed moderate intercellular edema.

In the dermis a cellular infiltrate, which was denser about blood vessels, hair follicles and sweat glands, was present. It was made up of polymorphonuclear leukocytes, lymphocytes and epithelioid cells. The walls of the capillaries showed endothelial hyperplasia, and about many of them there was a deposit of an eosinophilic "toxic hyalin," but the vessels were not occluded. The dermis was moderately edematous.

## COMMENT

The histopathologic criteria for the diagnosis of erythema elevatum diutinum as set forth by Weidman and Besancon [2] are moderate acanthosis in the epidermis and acute toxic periarteritis and peritelangiitis in the dermis. Polymorphonuclear leukocytes are abundant about the blood vessels in the dermis, and there is a toxic hyaline degeneration affecting the fibrous tissue about the capillaries. This degeneration is not as extensive as in early lesions but is regarded as characteristic for the disease in the later stages.

In case 1 microscopic examination of biopsy specimens taken ten years apart revealed these characteristic changes. In the earlier specimen a cellular infiltrate, made up predominantly of polymorphonuclear leukocytes, was present in the dermis. The walls of many of the blood vessels showed endothelial hyperplasia, and a zone of "toxic hyalin" was observed about many of them, but there was no occlusion of the lumens. In the more recent specimen there was a less dense perivascular cellular infiltrate, in which polymorphonuclear leukocytes were greatly decreased in number. The changes in the vessel walls were similar to those in the earlier specimen, but there was evidence of fibrosis in the dermis. The first specimen probably represents a well developed lesion, and the second, an older lesion.

Microscopic examination of the biopsy specimen taken in case 2 revealed changes similar to those observed in case 1, but less extensive.

This specimen presented the picture described by Ketron [5] as characteristic of an early lesion; a dense cellular infiltrate, consisting mostly of polymorphonuclear leukocytes, endothelial hyperplasia in the blood vessels, and a slight deposit of "toxic hyalin" about some of the vessels.

In the third case deposits of "toxic hyalin" are more conspicuous than in case 2, but not so extensive as in case 1. There was a dense perivascular infiltrate in which polymorphonuclear leukocytes predominated. The changes present compared closely with those described by Ketron [5] in biopsy 2 on his patient, the specimen for which examination he considered to be from a well developed lesion.

The clinical changes in 2 of the 3 patients presented were similar to those in the cases previously reported by other authors. There were more or less persistent, red to purple nodules, with some tendency to grouping about joints. However, an examination of the third patient, the 5 year old girl, revealed only a very few papules over the thighs and buttocks.

The third case was also unusual because of the age at which the eruption appeared. In all the previously reported cases, the patients were more than 30 years old at the time they were studied,[6] and none of these patients gave any history of the appearance of the eruption in early childhood. Patients 1 and 2 of this report were 56 and 59 years of age, respectively, while the third patient was only 5 years old.

Two of the 3 patients responded well to treatment. They were treated with foreign protein therapy and were apparently cured at the time of the last observation. The third patient has not been treated as yet. Weidman and Besancon noted that the lesions of one of their patients improved after antityphoid vaccination and expressed the opinion that the improvement was due to a nonspecific protein effect. Engman, Pfaff and Cooper used miid foreign protein therapy in their case and noted that many of the lesions disappeared after this treatment.

Barnard Skin and Cancer Hospital.

## ABSTRACT OF DISCUSSION

Dr. Fred D. Weidman, Philadelphia: I wish first to take this opportunity of giving a follow-up report on the patient of mine to whom Dr. Weiss alluded. I have seen the man from time to time, the last time about three months ago. The lesions have regressed to mere areas of pigmentation, and for several years there have been no exacerbations. The patient is still mildly psychotic, and I have always felt that his psychosis had a basis in the general toxemia which he must have, and which is reflected in the histopathologic change in the skin.

It must be remembered that the histopathologic picture alone is not always self sufficient for the establishment of an entity, and in this connection I would

6. Crocker and Williams.[1] Weidman and Besancon.[2] Combes and Bluefarb.[3] Engman, Pfaff and Cooper.[4]

cite the nodular perivasculitis reported by O'Leary and Montgomery, with histopathologic changes somewhat similar to those of erythema elevatum diutinum. I believe that minor variations in the tissue reaction should not be given too much weight. I dare say that if, instead of one biopsy, four or five were made on the same patient, there might be as much difference among the pictures presented by them as there is between nodular perivasculitis and erythema elevatum diutinum. In short, the "toxic hyalin" should not be given such weight as to be of itself sufficient to establish an entirely separate entity, but when one adds to that the over-all picture—the progress of the disease, the duration and the gross morbid anatomy—then I think that one is entirely justified in accepting erythema elevatum diutinum as a separate entity.

I did not hear anything said in this presentation about arthritis, such as was present in my 2 cases. Again, I do not think that arthritis is an essential feature of this entity. It is a manifestation of toxemia that is in the picture. It is a part of the case. There is no reason that the joints should be affected in some cases and not in others.

In short, I think that one should be content with looking at erythema elevatum diutinum simply as an expression of a general constitutional toxemia, leaving the scope of the disease large enough to include cases which present the arthritic syndrome.

DR. LOUIS H. WINER, Beverly Hills, Calif.: In teaching graduate students, I have frequently been confronted with the question: "What do you think about erythema elevatum diutinum?"

It has been my opinion that it is an entity closely allied to, if not the same as, granuloma annulare. However, cases have been reported some of which could be interpreted as "knuckle pads" and others as necrobiosis lipoidica diabeticorum. I agree with Dr. Weidman that the histologic picture here is not characteristic of any specific disease. The same changes are seen in many diseases of the vessels and also in toxemia.

The histologic sections could have called forth the diagnosis of drug eruption, erythema multiforme or even a mild form of periarteritis or perivasculitis. Therefore I cannot classify erythema elevatum diutinum as a specific histologic entity on the basis of anything shown today.

DR. FRANK C. COMBES, New York: I wish to report on a patient I first saw almost ten years ago (Combes, F. C., and Bluefarb, S. M.: Erythema Elevatum Diutinum, ARCH. DERMAT. & SYPH. **42**:441 [Sept.] 1940). New lesions have since developed in this case, and the original ones have become progressively larger and firmer. The patient has been treated with roentgen radiation, without the slightest benefit. I have the same results in another case. I therefore am interested in Dr. Weiss's report.

Erythema elevatum diutinum is undoubtedly a clinical entity, independent of granuloma annulare. Unfortunately, when Crocker and Williams wrote an article on this dermatosis, they included a case described by Bury in 1889, which was apparently one of granuloma annulare. Graham Little, in making a survey in 1908, concluded that erythema elevatum diutinum was a subvariety of granuloma annulare, but the cases he collected were mostly of the Bury type. In 1932 Little agreed that the two conditions were distinct, which opinion is generally accepted today.

DR. FRANCIS A. ELLIS, Baltimore: Dr. Ketron's patient with erythema elevatum diutinum received roentgen therapy, without any noticeable effect on the lesions.

If one obtained a typical section from a case of fully developed erythema elevatum diutinum, trained dermatohistopathologists would be in about 100 per cent agreement on the histologic diagnosis. It is not unusual to see sections in which the picture is that of erythema elevatum diutinum in that there is a fairly dense infiltrate of well preserved polymorphonuclear leukocytes in and about the wall of the blood vessels but not the "toxic hyalin" in the vessel wall. These lesions may represent chronic nonsuppurative pyoderma of the cutis.

Dr. Richard S. Weiss, St. Louis: In regard to Dr. Weidman's point about the resemblance of this condition to perivasculitis, if both the microscopic picture and the clinical picture are considered, the two diseases can be differentiated. None of our patients had actual arthritis. The little girl complained of growing pains. One of the men patients stated that his mother had had rheumatic arthritis, and he complained of pains in the joints whenever he had a bout of fever.

Dr. Winer, one must consider granuloma annulare in the differentiation of this condition. Blood sugar determinations were made in the cases of the 2 men, but not in that of the little girl, and the values were within normal limits. It is generally accepted that in cases of granuloma annulare the lesions, after they once appear, may disappear for months, and sometimes years, but there are relapses.

Roentgen irradiation, Dr. Combes, was used as adjunct therapy with these patients and was followed up with more protein therapy. The 2 men made an almost complete recovery with residual lesions in some areas, which lesions were treated with superficial roentgen therapy.

One wonders why Dr. Weidman and the other workers took the name of erythema elevatum diutinum for this complex disease, which seems to be entirely different from the eruption described by Crocker. Crocker referred in his article to the previously reported cases which resembled his. I get the impression that the condition in the cases described by Crocker and previous workers were probably granuloma annulare.

I agree with Dr. Ellis that when the histopathologic picture shows the infiltrate consisting of polymorphonuclear leukocytes this complex disease is to be suspected.

# HISTOPATHOLOGY OF ATOPIC DERMATITIS AND CHARACTERISTIC ATOPIC REACTION TO PATCH TEST

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AND
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THE CHARACTERISTIC atopic reaction to patch tests with human dander and the naturally occurring lesions of the disease atopic dermatitis resemble each other grossly in the occurrence of papules, papulovesicles, redness and slight desquamation and in their chronologic development and retrogression. The natural lesions, of course, are frequently modified by trauma and sometimes by secondary infection.

Since the allergen of human dander has been found to be present not only in the scalp but also in the skin of the general body surface,[1] it must be given consideration as a possible clinically important allergenic excitant of the disease. Hence it is desirable to study further, by histologic methods, the similarities and dissimilarities of the natural lesions and the reactions to patch tests.

## PRESENT INVESTIGATIONS

*Method and Material.*—This study is based on biopsies made of 14 specimens obtained from 9 patients with atopic dermatitis, aged 6 and 14 months and 5, 5, 6, 8, 14, 15 and 29 years. Sections of natural lesions were removed from all 9 patients. Specimens showing reactions to patch tests were obtained from 5 patients, 3 of the specimens being of patches on normal skin and 2 of patches on scarified skin. The sections of skin were removed with a biopsy punch, fixed in dilute solution of formaldehyde U. S. P. (1:4), stained with hematoxylin and eosin and cut in serial section so that small lesions, such as papules, could be followed throughout their entire course. The dander used for the patch tests was obtained from a normal scalp and mixed with sufficient petrolatum to make a thick paste. The patch remained in contact with the skin for two days, and the sections of skin were removed six hours (in 3 cases), two days (in 1 case) and seven days (in 1

From the Departments of Medicine, Bacteriology and Immunology and Pathology of the University of Louisville School of Medicine.

1. Simon, F. A.: The Allergen of Human Dander Present in Skin of the General Body Surface, J. Invest. Dermat. **9**:329, 1947; The Allergen of Human Dander: Its Relative Concentration in Several Skin Areas and in Appendages, Products and Derivatives of the Epidermis, ibid. **11**:203, 1948.

case) after removal of the patch. Patch tests with egg white, dwarf ragweed pollen, feathers and petrolatum had negative reactions in these 9 patients. In tests on other series of patients, however, reactions similar to those reported here have been produced, in a few cases, by egg white and ragweed pollen.

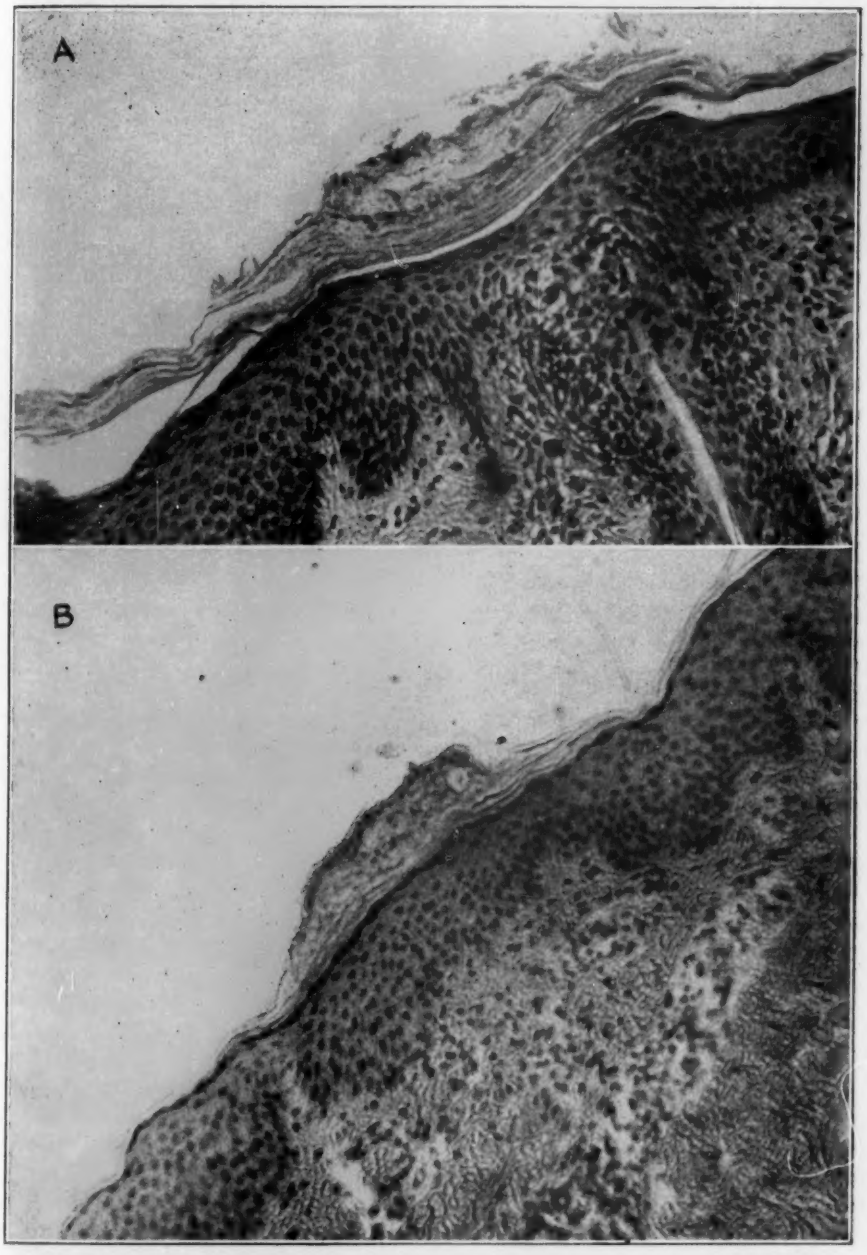


Fig. 1 (patient 3).—*A*, reaction to patch test with human dander in a child 5 years of age. Section was removed nine days after application of the patch. *B*, natural lesion of atopic dermatitis in the same child.

*Results.*—Natural Lesions: There were localized areas of parakeratosis in which the stratum corneum was thickened; the cell nuclei were pyknotic, shrunken and irregular in shape. The cytoplasm took the pink stain with eosin and in some areas was vacuolated and granular. In some lesions the surface had a ragged appearance and the surface cells a

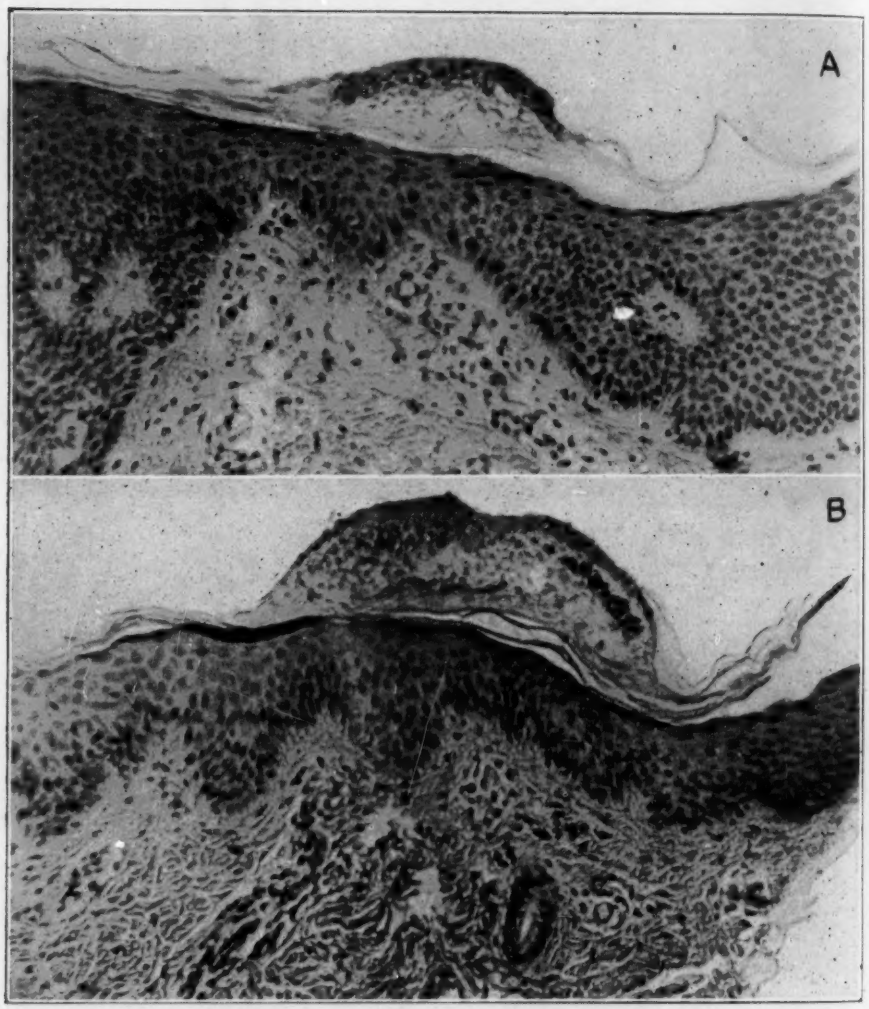


Fig. 2 (patient 4).—*A*, reaction to patch test with human dander in a child 5 years of age. Section was removed four days after application of the patch. *B*, natural lesion of atopic dermatitis in the same child.

brownish discoloration. Underlying the areas of parakeratosis the stratum spinosum was, in some cases, edematous and occasionally contained vesicles. An occasional polymorphonuclear leukocyte could be seen in some areas of parakeratosis and also in the stratum spinosum.

In some areas mitotic figures in the stratum germinativum appeared to be more abundant than normal. The underlying dermis was edematous and infiltrated with lymphocytes.

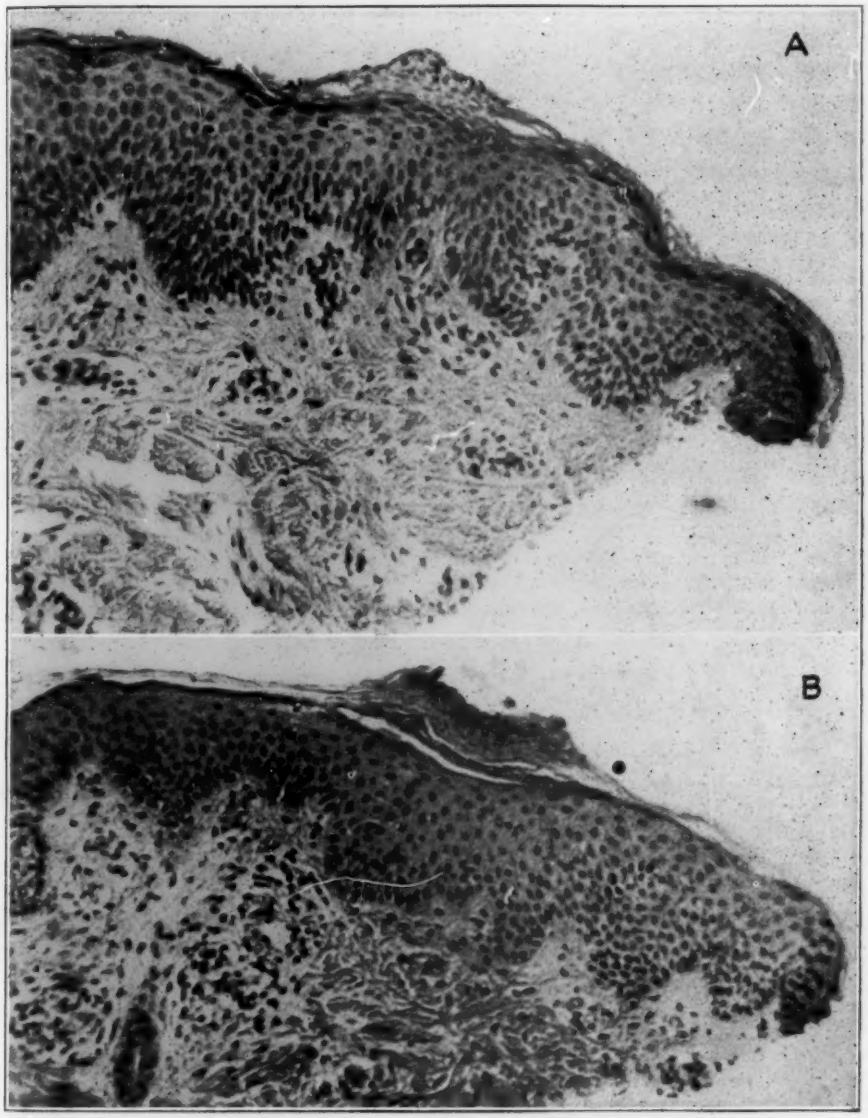


Fig. 3 (patient 2).—*A*, reaction to patch test with human dander in a child 14 months of age. Section was removed four days after application of the patch. *B*, natural lesion of atopic dermatitis in the same child.

Reactions to Patch Test: The older and less severe reactions showed areas of parakeratosis similar to those described in the pre-

ceding section. The earlier and severer reactions had definite vesiculation of the epidermis. In the case of patch tests on normal, unscarified skin the reactions, unlike the natural lesions, were located in and adjacent to hair follicles and the ducts of sweat glands. In the case of patch tests applied on scarified skin the reaction was located in

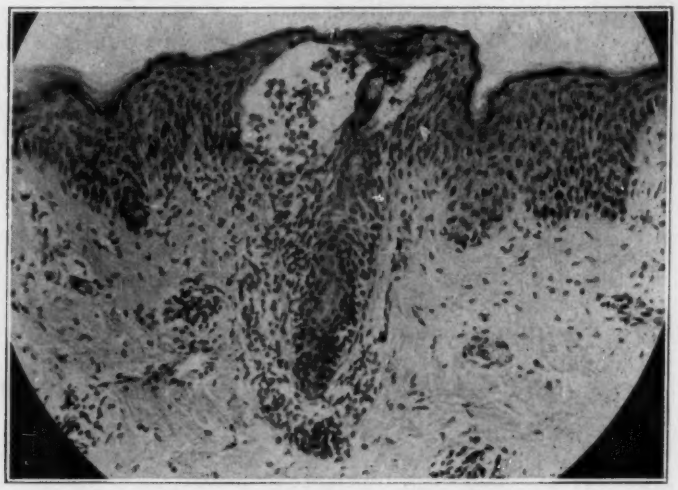

Fig. 4 (patient 8).—Reaction to patch test in a patient 15 years of age, illustrating an early, severe, acute lesion adjacent to the duct of a sweat gland. Section was removed two days and six hours after application of the patch.

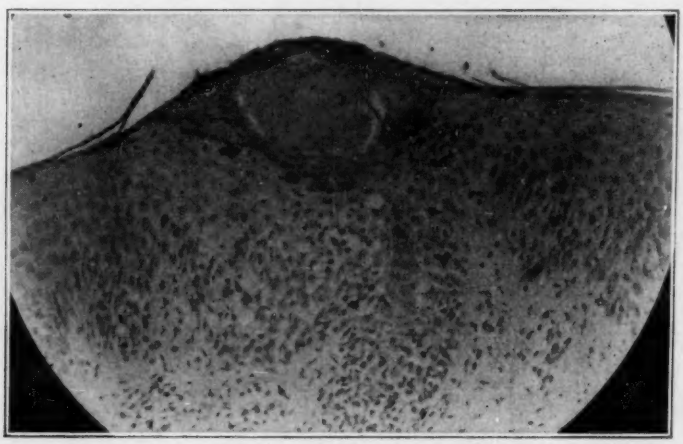

Fig. 5 (patient 1).—Natural lesion of atopic dermatitis in a child 6 months of age. This and figure 4 illustrate extreme differences in intensity and chronicity.

the epidermis adjacent to the scratch, regardless of hair follicles or sweat gland ducts. The dermis was edematous and infiltrated with lymphocytes.

COMMENT

The natural lesions and the reactions to patch tests have much in common. They involve the same tissues, with the same type of reaction. That the reactions to patch tests should be somewhat more acute and destructive is to be expected because they are produced by dander from the scalp, which contains a much higher concentration of allergen than the skin of the general body surface.[1]

In the case of patch tests applied on normal, unscarified skin the location of the reactions in and adjacent to hair follicles and the ducts of sweat glands may be explained on the basis of penetration of the allergen, which gains entrance to the epidermis most readily through the natural orifices of the skin. The protection from penetration of the allergen afforded by the cornified layer is further demonstrated by the reactions to patch tests applied on scarified skin, in which the lesion occurs in the epidermis adjacent to the scratch regardless of gland ducts or hair follicles, and also by the reactions in hair follicles, which changes are most pronounced in the lower part of the follicle, where the cornified layer is absent, even though this part of the follicle is more distant from the site of application of the patch. In other words, there are slight differences in the location of the reactions and in their intensity and chronicity which may be explained on the basis of variations in the point of application of the allergen and in its concentration. In the natural lesions the allergen may be present, exert its influence and even arise somewhere beneath the surface of the skin. Attempts to identify the allergen in microorganisms cultured from the skin have been unsuccessful.[2] Because of this fact, and also because the allergen has been identified in the epidermis of a newborn infant, we must consider the possibility that it arises in and from the skin itself. In this connection there are two locations in the skin deserving of consideration—locations in which cells are undergoing degeneration. These are (1) the sebaceous glands, which, being holocrine glands, secrete by pushing cells toward the lumen of the gland, where the whole cell degenerates into sebum, and (2) the region of the stratum granulosum and the stratum lucidum, where epidermal cells are degenerating to form the stratum corneum. In both locations, cells are dying, protoplasm is changing chemically and hence there is opportunity for the formation of a "foreign substance" in the body. The slight evidence available from the histopathologic picture points to the stratum granulosum–stratum lucidum area rather than to the sebaceous glands. The question then arises: Can the cells of the stratum lucidum and stratum granulosum be sufficiently dead to produce a foreign allergenic substance and yet

2. Simon, F. A.: On the Allergen in Human Dander, J. Allergy **15**:338, 1944.

sufficiently alive to react allergically to its presence? The deeper reactions in the stratum spinosum may, of course, be due to allergen which has penetrated into this level from overlying layers.

SUMMARY

The natural lesions of atopic dermatitis and the cutaneous reactions to patch tests with human dander both show areas of parakeratosis in which the nuclei of epidermal cells are pyknotic, shrunken and irregular in shape and the cytoplasm pink staining and in some cases granular and vacuolated. Beneath some of these areas the stratum spinosum is edematous and in some cases vesicular. The dermis is edematous and infiltrated with lymphocytes.

The reactions to patch tests are somewhat more acute and destructive and are located in and adjacent to hair follicles and the ducts of sweat glands. These differences in the location of the reaction and in its intensity and chronicity are explained as being due to variations in the concentration, penetration and site of application of the allergen.

Heyburn Building (2).

# HERXHEIMER REACTIONS IN PENICILLIN TREATMENT OF SYPHILIS IN PREGNANCY

JACK H. BOWEN, M.D.

H. N. COLE, M.D.

J. R. DRIVER, M.D.

RICHARD C. LIGHT, M.D.

AND

JOHN E. RAUSCHKOLB, M.D.

In Collaboration with M. H. Gustafson, M.D., Burt Held, M.D., J. M. Kam, M.D., Manly Utterback, M.D., and A. E. Walker, M.D.

CLEVELAND

SINCE October 1943 treatment with sodium penicillin has been carried out in a total of 182 cases of pregnancy complicated by early syphilis at the Cleveland City Hospital and the University Hospitals. Although total doses of penicillin increased as time went on from 60,000 to 9,600,000 units, in the bulk of the cases (86 per cent) at least 2,400,000 units were given in divided doses every three hours for from sixty to one hundred and twenty injections. The results of treatment are measured in terms of the efficacy of penicillin in protecting the fetus or, better, in curing the fetus of the maternal infection.

In this study there were 5 cases of primary syphilis, 63 cases of secondary syphilis and 114 cases of early latent syphilis. Excluded were all cases of patients thought to have had adequate treatment who were re-treated for protection of the fetus, and all late latent cases.

In a study of this kind the value of the results obtained depends largely on follow-up examinations over prolonged periods. By perseverance and unlimited effort, the rate of follow-up examinations on children born to syphilitic mothers was raised from 21 per cent in November 1946 to 96 per cent by May 1947.[1] Of the 182 mothers,

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From the Department of Dermatology and Syphilology, Western Reserve University School of Medicine, and of the Cleveland City Hospital and the University Hospitals.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Western Reserve University School of Medicine and under a grant-in-aid from the National Institute of Health, Syphilis Study Section, United States Public Health Service.

1. Mrs. M. K. Cooney, R.N.; Mrs. Gretchen Jeffery, R.N.; Mrs. Josephine S. Watkins, M.A., and Dr. Gerard DeOreo, Venereal Disease Control Officer, assisted in the observations on these children.

151 had active syphilis, 6 lapsed from observation and 25 are yet to be delivered. The observation period on the child extended over a period of one year before the case was considered closed. Ideally, an attempt should be made to examine these babies monthly for three months, again at six months, and, finally, at one year after birth.

The patients treated early in the series received a crude mixture of penicillin G, F and X containing not more than 100 to 200 Oxford units per milligram. Later, as the product was improved, the concentration rose to from 800 to 1,200 units per milligram. It is important to remember, however, that during the latter half of 1945 and the early half of 1946 the supplies of penicillin contained a high percentage of the K fraction rather than the G, F and X fractions. The K fraction is known to be rapidly destroyed and excreted by the body and thereby is less effective than the G fraction.

## CONGENITAL SYPHILIS

Of the 182 cases of syphilis complicating pregnancy, there were 4 cases of congenital syphilis. The mothers of these babies all had acute secondary infections when penicillin therapy was instituted. These 4 cases are presented briefly:

### REPORT OF CASES

CASE 1.—V. L., with a generalized syphiloderm, was treated in the seventh month of pregnancy. She received 300,000 units of penicillin sodium, given in doses of 5,000 units every three hours for sixty injections. Delivery occurred forty-two days later. The mother had an essentially negative serologic reaction one month after delivery. However, the child's blood one month after birth showed rising titers in all qualitative tests, and two months after birth the infant had seroclinical syphilis, with a severe meningeal type of syphilitic changes in the spinal fluid. Nine months later the mother was serologically negative and clinically well and then was lost to further follow-up observation. The child's symptoms responded well to treatment with penicillin, but both mother and child moved out of town seven months post partum.

CASE 2.—D. W. was treated in the sixth month of pregnancy for a papular syphilid. She received 9,600,000 units of penicillin sodium, given in doses of 80,000 units every three hours for one hundred and twenty injections. This penicillin contained a high percentage of the K fraction. The child was born two months after treatment and had a positive serologic reaction of the cord blood. Two months after birth the child's blood showed 16 Kahn units. This reaction persisted, and by the third month snuffles, diarrhea and hepatomegaly had developed. The child was given penicillin therapy and became clinically and serologically free from disease, only to die of pneumonia at the age of 7 months. In the mother in this case, dark field–positive vulvar lesions developed two months after delivery.

CASE 3.—E. W. was treated in her first month of pregnancy for a maculopapular secondary syphilid. She received 1,600,000 units of penicillin sodium, given in doses of 20,000 units every three hours for eighty injections. The child was delivered at term and was clinically well. Ten weeks after birth, the baby's

blood showed 64 Kahn units, and the child had a papular eruption, a nasal discharge, hepatomegaly, splenomegaly and roentgenologic evidence of periostitis of the long bones. The infant was treated with penicillin and was serologically and clinically well on examination seventeen months afterward. The mother, who had been lost to observation until delivery, was found to be seropersistent and was started on long term therapy.

CASE 4.—M. G., with secondary syphilis, was treated in the third month of pregnancy with 4,800,000 units of penicillin sodium, given in doses of 80,000 units every three hours for sixty injections. This penicillin again contained an excess of the K fraction. When the child was 2 months old, the serologic test showed 64 Kahn units. The infant also had snuffles, hepatomegaly, splenomegaly and rhagades. Roentgenograms of the long bones showed an osteochondritis consistent with syphilis of the bones. The child received a total dose of 550,000 units over a period of two weeks and was completely cured thirteen months afterward. The mother had a serologic relapse nine months after treatment and was placed under standard therapy.

## REACTION TO PENICILLIN

The reactions noted in this series of cases were usually minimal: urticaria and febrile Herxheimer reaction. The first may be adequately controlled with diphenhydramine hydrochloride (benadryl hydrochloride®) or tripelennamine hydrochloride (pyribenzamine hydrochloride®), and in no case was it necessary to discontinue penicillin therapy.

However, in 2 cases it is felt that a serious reaction in the form of a placental or fetal Herxheimer reaction occurred, with resulting premature labor and the delivery of a stillborn fetus. Claim has been made that penicillin is innocuous to the child when a pregnant syphilitic woman is treated. Only Ingraham [2] has raised some question regarding this point.

## REPORT OF CASES

CASE 5.—C. W., in the sixth month of pregnancy, with extensive moist papules and 64 Kahn units, received a total dose of 9,600,000 units of penicillin sodium, 80,000 units being given every three hours for one hundred and twenty injections. She had a grade II Herxheimer reaction. Fetal movements were felt at the onset of treatment; however, after the end of the first day of treatment, neither the mother nor the examining physician was able to detect movement, and no fetal heart tones were heard. Seven days after the end of treatment with penicillin, the mother, who had already gone home after discontinuance of therapy, was delivered of a stillborn fetus.

CASE 6.—The case of B. K. was similar. She was in her seventh month of pregnancy and had an extensive syphiloderm with dark field–positive moist papules, despite the fact that she had had eight intravenous treatments with penicillin, given irregularly by her family physician, the last one only three weeks previously. She received 9,600,000 units of penicillin, given in doses of 160,000 units every three hours for sixty injections. Her temperature rose from 36.8 to 37.8 C. (98.2 to 100 F.) and dropped in three hours to 36.8 C. She complained of absence of fetal movements after twenty-four hours, and examination revealed absence of

2. Ingraham, N. R., Jr.: Penicillin Treatment of the Syphilitic Pregnant Woman, J. A. M. A. **130**:683-688 (March 16) 1946.

fetal heart tones. The patient left the hospital on the eighth hospital day and was admitted to the delivery room in another hospital ten days later, at which time she was delivered of a macerated fetus.

In neither case was it possible for us to get an examination of the dead fetus.

### SUBSEQUENT PREGNANCIES IN PENICILLIN-TREATED SYPHILITIC MOTHERS

Another interesting feature of this series of cases is that of the mothers who were treated for syphilis with penicillin either during a previous pregnancy or at some time before the inception of pregnancy. Each of 7 mothers who were treated for early syphilis in one pregnancy had a normal child in a subsequent pregnancy without benefit of additional treatment. In 6 of our cases the mothers became pregnant after treatment with penicillin for various stages of early syphilis and were delivered of normal babies without further treatment.

Despite these 13 cases in which previous penicillin therapy apparently protected the baby in a subsequent pregnancy, the question arises as to what should be the practice concerning a pregnant woman with a history of syphilis.

Throughout this study are instances in which the penicillin cured the syphilis in the child and yet the mother later had a relapse. This result occurred in 44 of 151 cases, and there are 25 recent cases in which the mother is yet to be delivered. In many of the 44 known cases of relapse, penicillin in small doses was being employed, and, too, in some of these cases penicillin with a high proportion of the K fraction was being used.

Since penicillin therapy is a comparatively innocuous procedure, it is our feeling that in all cases of pregnancy complicated by a syphilitic infection, even though treated, the mother should have a course of treatment with penicillin. This would not necessarily require hospitalization, for such a mother could easily be treated in an ambulatory fashion by a semiweekly intramuscular injection into alternate buttocks of 600,000 units of one of the crystalline penicillin compounds in an absorption-delaying base. The initial dose should be small, and the total dosage, four to six injections.

### SUMMARY AND CONCLUSIONS

A series of 182 patients with early syphilis complicating pregnancy were treated with varying doses of penicillin sodium. Twenty-five of these patients have not yet been delivered; 6 have lapsed from observation, and 151 had active syphilis.

Four children were born with congenital syphilis in this group of 151 mothers with active syphilis.

An efficient follow-up procedure is a *sine qua non* in a clinic for "syphilis in pregnancy." Through great effort, it was possible for the

clinics represented in this study to raise their percentage of follow-ups within a period of nine months from an active average of 21 per cent to an active average of 96 per cent.

Penicillin seems to be almost a specific drug for syphilis in pregnancy, so far as the child is concerned, as may be seen from the reported results of only 4 cases of syphilitic children of the total of 151 cases of active maternal syphilis analyzed.

It is our feeling that in the present status of penicillin therapy it is advisable to treat the syphilitic woman in subsequent pregnancies, regardless of the physical and serologic findings. After all, penicillin therapy is a comparatively innocuous procedure.

In view of the large number of mothers—44 of 151 patients—who relapsed after delivery, frequent follow-up examinations of these women are essential. It is recommended that monthly examinations and titered blood tests be made until the patient has been serologically and clinically well for one year.

Two cases are presented of patients who were thought to have had serious fetal or placental Herxheimer reactions. In each instance fetal movements and a fetal heart tone present before treatment was started ceased within twenty-four hours after the institution of penicillin therapy. It is strongly felt that the dose of penicillin for the first twenty-four hours should be kept low, extremely low, to prevent such an occurrence.

# Clinical Notes

## INCIDENCE OF PSORIASIS

RICHARD L. SUTTON Jr., M.D.*
Professor of Dermatology and Syphilology, University of Kansas School of Medicine
KANSAS CITY, MO.

The incidence of psoriasis among the population at large was calculated by Gahan [1] at "not less than 1.0 per cent of the people living in and around New York." The basis for his figure was the fact that approximately 700 new cases of psoriasis were seen annually at the New York Skin and Cancer Unit. He estimated that "probably the Skin and Cancer Unit received no more than 10 per cent of the total number of patients who go for treatment to the various clinics in the New York Metropolitan Area," but he allowed, in arriving at a rough estimate, that even if that clinic received even as much as 20 per cent, "this would indicate a minimum figure of 100,000 for the number of persons suffering from psoriasis in and around the city of New York, an area containing approximately 10,000,000 population."

The Army General Hospital in the Zone of the Interior, where dermatologic service was supplied by me to both inpatients and outpatients, constituted a community of men of military age among whom it may reasonably be presumed that I saw every case of psoriasis. In the ten months from August 1943 to May 1944 there were 4,732 patients admitted to the hospital who were not admitted to the skin section. Of these, 10 persons, or 0.2 per cent, had psoriasis. There were in addition 201 patients admitted to the skin section, and of these, 3, or 1.5 per cent, had psoriasis. Army personnel of the detachment serviced by the dispensary comprised altogether approximately 1,000 persons, of whom 3, or 0.2 per cent, had psoriasis.

Psoriasis, accounting for roughly 1.5 per cent of cases of Army personnel hospitalized because of dermatoses, was far down on the list of common diseases of the skin, in contrast to its position second only to acne in order of frequency in the list of Bereston and Ceccolini,[2] whose report concerned dermatoses in 20,000 inductees. Psoriasis was found in only 0.2 per cent of persons, either hospitalized or on duty, who may be considered a random sample of the Army population.

### CONCLUSION

Gahan's figure of "not less than 1 per cent" is too high an estimate of the incidence of psoriasis, and 0.2 per cent is a figure more nearly approximating the truth.

411 Alameda Road (2).

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* Formerly Major, Medical Corps, Army of the United States, Chief of Section on Skin and Syphilis, Woodrow Wilson General Hospital, Staunton, Va.

1. Gahan, E.: Incidence of Psoriasis Among the Population at Large, Arch. Dermat. & Syph. **48**:305 (Sept.) 1943.

2. Bereston, E. S., and Ceccolini, E. M.: Incidence of Dermatoses in Twenty Thousand Army Induction Examinations, with Note on Syphilis with Negative Serologic Reactions, Arch. Dermat. & Syph. **47**:844 (June) 1943.

## STREPTOMYCIN OINTMENT IN TREATMENT OF SYCOSIS VULGARIS

HAROLD M. JOHNSON, M.D.
HONOLULU, HAWAII

Several months ago a former patient wrote to me regarding the cure of his recalcitrant sycosis vulgaris. This condition had been refractory to all topical medications, including penicillin ointment, quinolor® ointment,[1] ammoniated mercury ointment and wet dressings of tyrothricin. An ophthalmologist had casually mentioned that streptomycin ointment might be tried, as it had been successful in treatment of staphylococcic marginal blepharitis. In seven days the patient's skin was entirely clear, and it has remained so for six months at the time of writing.

An ointment containing 1,000,000 units of streptomycin powder per ounce (28 Gm.) of carbowax 1540® was used. This was vigorously applied before and after shaving and again at bedtime. Fifteen patients with sycosis vulgaris were treated. Duration of infection varied from two weeks to nine months. Cultures of infected hairs produced Staphylococcus aureus and Staphylococcus albus. In 12 cases there were good results, with clearing in from ten to twenty days. Itching usually subsided within the first week. No relapses were noted in three months. In 2 cases the patients had relapses after ceasing the streptomycin inunctions but remained free from symptoms while using the ointment. No cases of sensitization were noted in this small series.

Each patient was warned about the possibility of present and future allergic sensitization and about developing resistance to streptomycin. A recent report[2] demonstrated the possible epidermal sensitizing effect of the drug. Most of the patients previously had used many medicaments and were willing to take the risk of sensitization.

This antibiotic certainly is not the complete answer to this stubborn follicular infection, but it is suggested that it can be used as another helpful medicament in the therapeutic armamentarium.

1. Quinolor® compound ointment consists of equal parts of white petrolatum and wool fat, containing 10 per cent benzoyl peroxide and 0.5 per cent quinolor® (a mixture of 3 chlorine derivatives of 8-hydroxyquinoline).

2. Rauchwerger, S. M.; Erskine, F. A., and Nalls, W. L.: Streptomycin Sensitivity: Development of Sensitivity in Nursing Personnel Through Contact During Administration of the Drug to Patients, J. A. M. A. **136**:614-615 (Feb. 28) 1948.

## ANTITHYROID AGENTS

### Use in Treatment of Dermatitis Herpetiformis, Iododerma and Deep Mycotic Infection

THEODORE CORNBLEET, M.D.
CHICAGO

Recently certain synthetic materials have been found that oppose the formation of thyroxin, the active principle of the thyroid gland. This newer group consists of a number of substances, of which thiouracil and propylthiouracil have become the best known. The action of the thyroid gland is intimately connected with the metabolism of iodine since this element is utilized by and in a

From the Department of Dermatology, University of Illinois College of Medicine, and the Cook County Hospital.

sense serves to regulate the action of this endocrine structure. It was natural, therefore, to wonder whether the new antithyroid agents would affect dermatologic entities that are influenced by iodides.

Accordingly, 4 patients with dermatitis herpetiformis were treated with propylthiouracil.[1] They were given 100 mg. (2 tablets) three times a day, for ten days for 3 of the subjects and for seven days for 1. At the end of this time none was improved. One of the 3 had more lesions and complained of increased pruritus. The treatment of the fourth patient was interrupted at his insistence because of excessive itching. There were no untoward results otherwise. One patient who seemed to be uninfluenced clinically showed a drop in leukocyte count from 7,400 to 3,950, and the man who refused to continue after seven days of treatment because of increased itching had an increase of eosinophils from 2 to 9 per cent.

One patient with an acneform iododerma profusely distributed on the trunk and some lesions on the face was given a trial with propylthiouracil. She used 100 mg. (2 tablets) three times a day for eight days. There was no evident improvement in the eruption, nor was there any untoward reaction. Her urine at the end of this period still gave a strong qualitative reaction for iodides.

An opportunity is being awaited for a trial of propylthiouracil in treatment of a person with a deep mycotic infection who shows no favorable response to iodide therapy.

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1. The propylthiouracil used was supplied by Eli Lilly Co., Indianapolis.

# Society Transactions

## DETROIT DERMATOLOGICAL SOCIETY

James R. Rogin, M.D., *Chairman*
Hermann Pinkus, M.D., *Recorder*
*Nov. 20, 1946*

All cases were presented by Dr. Udo J. Wile and Dr. Arthur C. Curtis.

**A Case for Diagnosis (Poikiloderma?) in a Boy Aged 15 Years.**

**Xanthoma Tuberosum Multiplex in a Boy Aged 28 Months (One of Triplets, the Only One with the Disease).**

**Disseminated Sporotrichosis.**

R. F., a white man, aged 70, first noted an erythematous papule on the lower part of the back which became fluctuant and discharged purulent material about the middle of September 1946. Two more similar lesions developed within a few days—one on the right thigh and another on the right temporal region. He was given sixty-six injections of penicillin, during the course of which a widely disseminated eruption developed, consisting of red, slightly tender, furuncle-like lesions which discharged seropurulent material and cleared after a few days, only to be succeeded by new similar lesions.

The patient had no knowledge of an injury at the site of the first lesion. He had an epithelioma on the right cheek several years ago, which was treated by means of roentgen rays in another hospital.

The patient did not appear acutely ill. The eruption consisted of widespread, discrete, erythematous papules and papulopustules, varying in size from that of a green pea to that of a half-dollar. Some of these had ruptured and were covered with a crust. They were only slightly tender. The soft tissues of the right great toe, left forefinger and right fifth finger were swollen, red and tender to pressure.

Results of routine examinations of urine and blood were normal. The Kahn reaction of the blood was negative. Results of sternal marrow examination were interpreted as indicative of malignant reticuloendotheliosis. Numerous biopsies of cutaneous lesions demonstrated "mixed tuberculous and pyogenic granulation tissue." Cultures grown from three widely separated lesions showed a pure culture of Sporotrichum schenckii. The patient was treated with potassium iodide by mouth.

DISCUSSION

Dr. Arthur Schiller: I wonder in cases of this kind why blood cultures should not show organisms and why there is no pulmonary or other organ involvement? I do not believe that the lesion on the face is the same as the lesions on the body.

Dr. Harther Keim: I wondered about the possibility of a disseminated deep fungus infection. Some of the other lesions which were partially ulcerated sug-

gested sporotrichosis, but I have never seen a disseminated type of the disease before.

DR. UDO WILE: I saw this patient when there were large tumors along the arms which closely resembled abscesses. The pathologists offered little in the way of information. It was diagnosed as tuberculosis but could not have been this. All the larger growths have disappeared with treatment. The finger lesions have healed. All involvement is not only that of soft tissue, but the roentgenograms show bone changes in both the right index finger and the right first toe. This is a unique case of sporotrichosis.

DR. HERSCHEL ZACKHEIM (by invitation): I have found that serial dilutions of Sabouraud's 4 per cent dextrose broth containing concentrations of streptomycin as high as 256 units per cubic centimeter failed to inhibit the growth of Sporotrichum schenckii.

DR EDWARD CAWLEY (by invitation): The cultures from the lesions of this man were planted, and for several days nothing was seen. The day he was ready to go home, the growths were large enough to be of significance. Dr. Schiller spoke of blood cultures. We had no opportunity to do these because we did not find that he had sporotrichosis until too late. Lewis and Hopper (An Introduction to Medical Mycology, Chicago, The Yearbook Publishers, Inc., 1938, p. 168) described a subcutaneous disseminated type of sporotrichosis; apparently this disease occurs in France with a fair degree of frequency but is extremely rare in this country. This man has a pulmonary lesion, the nature of which was not clarified by the roentgenograms.

**Generalized Progressive Scleroderma.**

H. J., a white woman aged 42, was first seen at the University Hospital in October 1941, with the complaint that during the previous eight months she had had swelling and muscular pain and tenderness of her extremities. An increased sensitivity to heat and cold had also been noted, and the hands had recently shown cyanotic tendencies in cooler temperatures. Edema of the face, which appeared from time to time, was also mentioned by the patient. The examination here demonstrated little more than the fact that application of external heat to the hands and feet caused vascular dilatation. The digits were described as "cold, wet, thickened and mildly edematous." Muscular weakness and tenderness were found greater in the right than in the left extremity. Hyperesthesia and increase of reflexes were also more pronounced on the right. Pigmentation in the few areas exposed to light was excessive. Laboratory observations were normal at that time, and results of biopsy of skin and muscle taken from the calf were inconclusive. The patient left our care but returned in February 1946. The disease had gradually progressed, and she then complained of intense pruritus together with fixation of the skin, not only of the extremities but also of the face, with some difficulty in swallowing. Pigmentation had become extensive and pronounced.

In childhood the patient had had diphtheria and scarlet fever. At 18 years she had had pleurisy. At 27 a hysterectomy with a left oophorectomy was performed, and at 33 a gastric stricture was relieved surgically. The family history was not contributory.

Almost the entire integument was involved by a mottled brown-gray pigmentation. The skin of the extremities and neck was particularly hidebound and thickened. There was some facial restriction of motion, particularly about the mouth. A few urticarial papules and excoriations were seen on the extremities. The Kahn reaction of the blood was negative.

The patient was given a long regimen, consisting of ammonium chloride, 6 Gm. in three day courses, with three days of rest between courses. Diphenhydramine hydrochloride (benadryl hydrochloride®), 200 mg. daily, was also administered. By August 1946, the patient reported increased motility of the arms and greater laxity of the skin about the face. The skin on the extremities and face was objectively much less hidebound. Many more excoriated papules were seen about the back, abdomen and wrists. Benzyl benzoate lotion was prescribed, with complete relief from the itching.

DISCUSSION

DR. ARTHUR SCHILLER: I should like to ask Dr. Curtis whether he is of the opinion that diphenhydramine hydrochloride (benadryl®) is superior in treatment of this disease?

DR. ARTHUR CURTIS: The patient is receiving ammonium chloride, 6 Gm. for three days followed by omission of the drug for three days, and she is also receiving benadryl.® In scleroderma an early change in the skin is a deposit of calcium. In later stages this may produce calcinosis. In an attempt to decalcify the skin ammonium chloride is given, as mentioned before. Many of these patients have said that they have some softening of the skin. The Mayo Clinic is using benadryl® in the treatment of scleroderma. I cannot say with certainty whether or not any of this woman's improvement is due to benadryl.®

DR. JAMES ROGIN: One year ago, Dr. Paul O'Leary was using benadryl® in the acute edematous stages.

DR. HERSCHEL ZACKHEIM (by invitation): At Receiving Hospital 1 patient with advanced scleroderma was given benadryl,® 480 mg. daily for over three months, with no noticeable improvement.

**A Case for Diagnosis (Ehlers-Danlos Syndrome and Lupus Erythematosus?).**

**Linear Nevus (Ichthyosis Hystrix).**

**Atrophoderma Maculatum (Anetoderma of Schweninger and Buzzi).**

**Tuberculosis Luposa.**

L. P., a white man aged 28, was well until seven years ago, when he noted a swelling in the anterior portions of the neck; this was incised, resulting in a discharging sinus. Since that time similar lesions have appeared on the neck and ankles. In 1943, he noted a crusting eruption on the face, which became more extensive, produced considerable scarring and persisted, despite sanatorium care. Development of a carcinoma in an old scar on the nose resulted in amputation of the nose a few years ago. The family history is not significant.

Examination of the face some months ago showed a crusted and ulcerated eruption, with extensive scarring. Apple-jelly nodules were apparent on diascopy. Pigmented scars were present at the suprasternal area and on the ankles.

Results of blood cell counts and urinalyses have always been normal. Repeated roentgenograms of the chest have been normal. The Kahn reaction of the blood was negative. At least one of several biopsies of the face demonstrated tuberculous granulation tissue. For several months the patient has received 300,000 units of vitamin D each day with decided improvement of the face.

DISCUSSION

DR UDO WILE: This man has lupus vulgaris. He has an amazingly long history of the disease. Three years ago he had a small lesion on the nose which was erroneously diagnosed in the laboratory as carcinoma. The nose was ablated. Three months ago he had numerous tuberculous nodules on the face and a large ulcerated tuberculous lesion at the angle of the mouth. He was given 300,000 units of irradiated ergosterol and 6 Gm. of calcium gluconate daily. The lesions have all healed. This is the second case I have had, with the same amazing results. Successful treatment of lupus vulgaris with vitamin D was the outstanding dermatologic achievement to come out of Europe during the war.

DR. ARTHUR CURTIS: About three years ago the patient had his nose ablated; yet I feel sure that the changes were those of pseudoepitheliomatous hyperplasia and not epithelioma. His disease was so extensive that a diagnosis of leprosy was made in one of the state sanitoriums.

DR. LOREN SHAFFER: The question of the joint use of calcium with irradiated ergosterol arises. There is a theoretic possibility of one's producing calcinosis by such joint use. The English are not using such a combination. Since you have recently been in Europe, Dr. Wile, I wonder whether you have any further opinion.

DR. UDO WILE: I can only judge from the French experience, since they are using both, and with good results.

DR. ARTHUR CURTIS: It is known that irradiated ergosterol mobilizes calcium from the bones. Even though the patient was getting large doses of vitamin D, his blood calcium rose only to levels of 10.5 to 12 mg. per hundred cubic centimeters. High levels like this are not in the least dangerous.

**Multiple Idiopathic Hemorrhagic Sarcoma.**

**Poikiloderma Atrophicans Vasculare.**

**Cushing's Syndrome with Hidradenitis Suppurativa.**

M. P. was a white woman aged 48. In 1931, this patient's menstrual flow became scanty, and she noticed a decided increase of bodily hair and the growth of a beard. A short time later, painful furuncle-like lesions developed at the sides of the nose and in the axillas, groins and gluteal cleft. During subsequent years she has continued to have lesions at the sites mentioned, and bodily hair growth has become excessive, necessitating, on the face, daily shaving. The family history is not significant.

Examination showed hypertrichosis of the face, back and chest. Lesions of hidradenitis suppurativa are present on the face and breasts and in the axillas and perineal regions. The blood cell count was normal with the exception of 16,000 white cells. The differential count was normal. The Kahn reaction of the blood was negative. The basal metabolic rate was plus 13 per cent. The result of the glucose tolerance test was normal. The rate of 17-ketosteroid excretion was 14.1 mg. per day. Roentgen examination showed a diaphragmatic hernia, minimal osteoporosis of the spine, calcification of a uterine fibroid and a normal skull. Excretory pyelograms showed no evidence of an adrenal tumor.

DISCUSSION

DR. HENRY BRUNSTING: In many patients with hidradenitis suppurativa there is usually associated acne of the face and back. I have always felt that there may

be some type of endocrine disturbance in these patients; however, I have never observed the association of Cushing's syndrome previously. Surgical measures, such as excision of the entire hairbearing area of the axilla followed by a full thickness graft should not be postponed too long. After this procedure I have seen other areas of involvement, such as the groin, improve spontaneously.

DR. ARTHUR CURTIS: I was glad to hear Dr. Brunsting make these statements, and I agree with what he says. I feel certain that this patient has a basophilic adenoma of the pituitary or Cushing's syndrome. She has a prominent hump of fat on the upper part of the back as well as decided hirsutism. Her blood pressure is slightly elevated and her bones slightly decalcified. The basal metabolic rate is also increased. No glycosuria is present, and there are no striae. She is 49 years old, and her condition came on suddenly. Roentgenograms of her sella turcica showed no pathologic changes, which is not uncommon. She was studied by Dr. Conn, the endocrinologist, who agreed with the diagnosis of Cushing's syndrome.

**James R. Rogin, M.D., *President***
**Hermann Pinkus, M.D., *Recorder***
***Jan. 15, 1947***

All the cases except the last two were presented by Dr. Frank Menagh and Dr. C. E. Reyner.

## Mycosis Fungoides with Ulcerated Granulomas and Psoriasiform Plaques. Five Cases of Tinea Capitis with Apparent Satisfactory Response to Treatment with Ointment of Copper Undecylenate.

DISCUSSION

DR. J. H. WELCH (by invitation): We have treated 12 patients with tinea capitis diagnosed by the Wood light but not by culture studies with an ointment containing copper undecylenate. Of the 12, 5 apparently have been cured (by the Wood light examination). The period of treatment has ranged from four months to three weeks. Nearly all had had previous treatment without effect. Three or four had epilation by roentgen rays. Of the 5 patients cured, 3 had not been treated by epilation and 2 had. We regard this as a fairly effective agent for handling the type of infection under discussion.

DR. LEE CARRICK: At the City of Detroit Receiving Hospital we have had some success with an ointment containing undecylenic acid, zinc undecylenate and sodium tetradecyl sulfate, a wetting agent (Carrick, L.: Methods of Local Therapy for Tinea Capitis Due to Microsporum Audouini, *J. A. M. A.* **131**: 1189-1194 [Aug. 10] 1946). With the undecylenic acid–zinc undecylenate preparation, used according to certain specific directions and in conjunction with a soap substitute, we were able to cure 40 per cent of 25 outpatients over an average treatment period of four and a half months. An additional 32 per cent were cured after a longer treatment period, bringing the total incidence of cures to 72 per cent.

DR. ARTHUR SCHILLER: I have been interested in the treatment of ringworm by various types of chemotherapy. We started with a copper oleate ointment, and the U. S. Public Health Service found in their Hagerstown experiment that copper oleate gave 37 per cent of cures. We then devised a copper propionate, and in the Hagerstown experiment this stood third in the list of drugs which gave relatively adequate results in ringworm treatment.

In our opinion, the results depend largely on the type of base in which the medicament is dispensed. In the Hagerstown experiment the first preparation on the list was salicylanilide ointment, which was credited with 57 per cent of cures. In the past seven months our results show only 46 per cent cures. Most of the treatments seem to effect improvement up to a certain point. Occasionally, when small stubborn patches are encountered, removing the hair with a standard barium sulfate paste seems to speed up the cure. Needless to say, the diagnosis should be checked by microscopic examination and culture.

DR. LOREN SHAFFER: At Wayne University Medical School we have worked with a grant from the Children's Fund of Michigan on this study. We have not got far beyond what you have heard. Not enough consideration is given to prevention of infection in other members of the family when one child has an infection of the scalp. I feel that the application of any unsaturated fatty acid once a week would be effective in prevention and might be used in the schools. It is felt that tincture of green soap, or any soap, should not be used daily. Using a strongly alkaline soap neutralizes the effect of treatment —removes the chemical preparation and the acid reaction. My advice is to use a soap substitute with a low $p_H$ value.

DR. HERMANN PINKUS: I realize that the situation in a small town is different from that in a large city like Detroit. In Monroe, Mich., a town of 20,000, we had an epidemic of approximately 150 cases in the winter of 1945-1946. Fortunately, the cases were confined almost entirely to one part of the town, in one public and one parochial school. There was fine cooperation from all authorities. All the children in the schools were checked systematically and repeatedly with the help of filtered ultraviolet rays, and infected children were kept out of school unless they were under medical care. During the height of the epidemic special classes were instituted for the patients. Most of the children were treated by roentgen ray epilation followed by antiseptic ointments. In several instances in which the parents did not agree to roentgen treatment at first or in which general practitioners handled the cases, the parents eventually asked for roentgen ray epilation when they saw the poor results of local therapy. When the schools reopened in the fall of 1946, the school authorities checked all the children within the first few weeks. Only a few patients with tinea capitis were discovered, and most of these had moved into town from other places during the summer.

DR. ARTHUR SCHILLER: I do not like to discourage Dr. Pinkus' optimism as far as the disappearance of ringworm in Monroe is concerned, but we have noticed a reduction in the number of cases in Detroit. In other sections of the country workers also have noticed a lessened number. I think that probably there is a certain degree of immunity established, but I am not at all convinced that another summer will not see a recrudescence of ringworm.

**Herpes Zoster with Ramsey Hunt's Syndrome.**

**Sudek's Atrophy of the Right Hand Following Herpes Zoster.**

M. V., a man, aged 60, was hospitalized in July 1946 with virus pneumonia, and after this herpes zoster of the right arm and hand, extending to the scapula, developed. There was much swelling of the fingers, with tenderness and inability to make a fist.

The vesicles appeared on the fingers of the right hand, up the anterior part of the forearm and the inner aspect of the arm to the scapula, in the

distribution of the fifth, seventh and eighth cervical nerves. The pain continued, with the patient unable to use the right hand. On Oct. 25, 1946, roentgenograms showed osteoporosis of both hands and wrists, most marked on the right. There was some atrophy of the muscles of the arm, weakness and fibrillary twitching. The fingers were painful, and the hand could not be closed.

There was osteoporosis of the right hand, with a worm-eaten appearance different from the diffuse osteoporosis of the left and characteristic of Sudek's atrophy.

Roentgen treatment of the involved ganglions, twenty intravenous injections of 100 cc. of 10 per cent sodium iodide and sedatives were given and had little effect on the course of the pain and disability. However, immediate improvement was experienced with the injection of tetraethylammonium chloride, 10 cc. of which was given twice daily for three days. There was no notable drop in blood pressure, and the improvement has continued. The swelling and the increased perspiration have disappeared.

DISCUSSION

DR. DANIEL BUCHANAN (by invitation): Sudek's atrophy is a condition in which, after an injury such as a fracture or sprain, there are severe pain and redness of the extremity and changes in the bone. The bone becomes mottled and decalcified. The bone picture alone is not diagnostic. It is seen also in many cases of fracture incurred in the war which required long immobilization. The disease is thought to be due to autonomic stimulation with vasodilatation, anoxia and further reflex stimulation of nerves and production of changes in the tissue. If you can break the cycle, you can cure the patient. One investigator used tetraethylammonium chloride with considerable success.

DR. ARTHUR SCHILLER: I should like to ask what benefit you have had from large doses of thiamine given intravenously.

DR. FRANK MENAGH: We have not used it recently. A few years ago, we treated a series of patients but were not impressed with its value.

DR. HERMANN PINKUS: I noticed that one of these men gave blood to another patient with herpes zoster.

DR. FRANK MENAGH: Dr. Trygve Gunderson found that if you give a blood transfusion early in herpes zoster ophthalmicus you can prevent damage to the cornea. (Convalescent Blood for Treatment of Herpes Zoster Ophthalmicus, *Arch. Ophth.* **24**: 132-141 [July] 1940.) I do not know that I ever saw a case of Bell's palsy clear up as rapidly as this.

**Melanosis (Riehl's?); Hyperpigmentation of Face and Arms.**

**Chronic Intercrural Dermatitis.**

**Dermatitis Medicamentosa, Fixed Type, from Arsenicals.**

**Dermatitis Medicamentosa Due to Neoarsphenamine.**

**Hydroa Vacciniformis in a Boy Aged 13 Years.**

**Sarcoidosis? Tuberculosis in a Negro?**

**Severe Hypoplastic Anemia Following Arsenical Therapy.**

**A Case for Diagnosis (Lupus Erythematosus? Pigmented Nevus?).** Presented by DR. GEORGE B. SEXTON, London, Ontario, Canada.

**Neurocutaneous Leprosy, Originating in a Tattoo.** Presented by DR. CLAUDE BEHN and (by invitation) DR. ROSS J. PORRITT.

L. G., a white man, was first seen on Nov. 11, 1946, complaining of a cutaneous lesion involving a tattoo and the surrounding area on the flexure surface of the left forearm and also two areas forming an hourglass shape on the extensor surface of the middle third of the left arm.

In June 1943 while a member af the United States Medical Corps, he was tattooed in Melbourne, Australia. Three years later he first noticed increased pigmentation and loss of superficial sensation involving the tattoo and the surrounding area. In a friend who was tattooed at the same time by the same person a similar lesion developed.

The skin of the entire tattoo and a zone 1.5 cm. in width about it shows a violaceous discoloration. There is a loss of pain and light touch sensation throughout the entire pigmented area. On the extensor surface of the left arm, 7.5 cm. above the elbow, there are two coalescent lesions making an hourglass-shaped area 2.5 by 4 cm. This has the same violaceous color as the tattoo area, and there is the same loss of sensation. There is no ulceration or elevation present and no palpable abnormality of the nerve trunks.

The reaction to intradermal injections of old tuberculin, 0.1 cc. in a dilution of 1 to 10,000, was negative. The Kahn reaction was negative. The blood and urine were normal. Guinea pig inoculation with tissue gave a negative result.

The skin and subcutaneous tissue show a tuberculoid reaction. There appears to be slight caseation in centers of some of the nodules. Fairly numerous well developed Langhans giant cells are present. The nodules extend through the corium into the subcutaneous fat. Occasional acid-fast bacilli were found by the Ziehl-Neelsen stain. They averaged not more than 1 per section.

DISCUSSION

DR. FRANK MENAGH: How was the leprosy transmitted?

DR. ROSS J. PORRITT (by invitation): It may be that the operator licked the needle.

DR. FRANK MENAGH: How about excising the area?

DR. ROSS J. PORRITT (by invitation): We discussed the possibility of excising it, but, considering the spread up above the elbow, we did not think it advisable. We did recommend that the boy go to Carville for six months, although the Health Department will not force him to go as long as there are no open lesions. Treatment with one of the new sulfone drugs may be tried.

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